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(54) Title: HYBRID POLYPEPTIDES WITH ENHANCED PHARMACOKINETIC PROPERTIES

N-terminal Interactive Region										C-terminal Interactive Region									
W	X	X	W	X	X	X	X	X	X	W	X	X	X	W	X	W	X		
W	X	X	W	X	X	X	X			X	X	X	W	X	W	X			
W	X	X	W	X	X					X	X	W	X	W	X				
W	X	X	W	X						X	W	X	W	X					
W	X	X	W									W	X	W	X				
										W	X	X	X	W	X	W			
										X	X	X	W	X	W				
										X	X	W	X	W					
											X	W	X	W					
												W	X	W					

(57) Abstract: The present invention relates to enhancer peptide sequences originally derived from various retroviral envelope (gp41) protein sequences that enhance the pharmacokinetic properties of any core polypeptide to which they are linked. The invention is based on the discovery that hybrid polypeptides comprising the enhancer peptide sequences linked to a core polypeptide possess enhanced pharmacokinetic properties such as increased half life. The invention further relates to methods for enhancing the pharmacokinetic properties of any core polypeptide through linkage of the enhancer peptide sequences to the core polypeptide. The core polypeptides to be used in the practice of the invention can include any pharmacologically useful peptide that can be used, for example, as a therapeutic or prophylactic reagent.

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HYBRID POLYPEPTIDES WITH ENHANCED  
PHARMACOKINETIC PROPERTIES

This application is a continuation-in-part of application Serial No. 09/350,641, filed July 9, 1999, which  
5 is a continuation-in-part of application Serial No. 09/315,304, filed May 20, 1999, which is a continuation-in-part of application Serial No. 09/082,279, filed May 20, 1998, the entire contents of each of which is incorporated herein by reference in its entirety.

10

1. INTRODUCTION

The present invention relates to enhancer peptide sequences originally derived from various retroviral envelope (gp41) protein sequences that enhance the pharmacokinetic  
15 properties of any core polypeptide to which they are linked. The invention is based, in part, on the discovery that hybrid polypeptides comprising the enhancer peptide sequences linked to a core polypeptide possess enhanced pharmacokinetic properties such as increased half life. The invention further relates to novel anti-fusogenic and/or anti-viral,  
20 peptides, including ones that contain such enhancer peptide sequences, and methods for using such peptides. The invention further relates to methods for enhancing the pharmacokinetic properties of any core polypeptide through linkage of the enhancer peptide sequences to the core  
25 polypeptide. The core polypeptides to be used in the practice of the invention can include any pharmacologically useful peptide that can be used, for example, as a therapeutic or prophylactic reagent. In a non-limiting embodiment, the invention is demonstrated by way of example  
30 wherein a hybrid polypeptide comprising, for example, an HIV core polypeptide linked to enhancer peptide sequences, is shown to be a potent, non-cytotoxic inhibitor of HIV-1, HIV-2 and SIV infection. Additionally, the enhancer peptide

sequences of the invention have been linked to a respiratory syncytial virus (RSV) core polypeptide and a luteinizing hormone receptor (LH-RH) core polypeptide. In each instance, the hybrid polypeptide was found to possess enhanced  
5 pharmacokinetic properties, and the RSV hybrid polypeptide exhibited substantial anti-RSV activity.

## 2. BACKGROUND OF THE INVENTION

Polypeptide products have a wide range of uses as therapeutic and/or prophylactic reagents for prevention and  
10 treatment of disease. Many polypeptides are able to regulate biochemical or physiological processes to either prevent disease or provide relief from symptoms associated with disease. For example, polypeptides such as viral or bacterial polypeptides have been utilized successfully as  
15 vaccines for prevention of pathological diseases. Additionally, peptides have been successfully utilized as therapeutic agents for treatment of disease symptoms. Such peptides fall into diverse categories such, for example, as hormones, enzymes, immunomodulators, serum proteins and  
20 cytokines.

For polypeptides to manifest their proper biological and therapeutic effect on the target sites, the polypeptides must be present in appropriate concentrations at the sites of action. In addition, their structural integrity must generally be maintained. Therefore, the formulation of  
25 polypeptides as drugs for therapeutic use is directed by the chemical nature and the characteristics of the polypeptides, such as their size and complexity, their conformational requirements, and their often complicated stability, and solubility profiles. The pharmacokinetics of any particular  
30 therapeutic peptide is dependent on the bioavailability, distribution and clearance of said peptide.

Since many bioactive substances, such as peptides and proteins, are rapidly destroyed by the body, it is critical to develop effective systems for maintaining a steady concentration of peptide in blood circulation, to increase the efficacy of such peptides, and to minimize the incidence and severity of adverse side effects.

3. 3.1. SUMMARY OF THE INVENTION

The present invention relates, first, to enhancer peptide sequences originally derived from various retroviral envelope (gp41) protein sequences i.e., HIV-1, HIV-2 and SIV, that enhance the pharmacokinetic properties of any core polypeptide to which they are linked. The invention is based on the surprising result that when the disclosed enhancer peptide sequences are linked to any core polypeptide, the resulting hybrid polypeptide possesses enhanced pharmacokinetic properties including, for example, increased half life and reduced clearance rate relative to the core polypeptide alone. The present invention further relates to such hybrid polypeptides and core polypeptides, and to novel peptides that exhibit anti-fusogenic activity, antiviral activity and/or the ability to modulate intracellular processes that involve coiled-coil peptide structures. Among such peptides are ones that contain enhancer peptide sequences.

Core polypeptides can comprise any peptides which may be introduced into a living system, for example, any peptides capable of functioning as therapeutic, prophylactic or imaging reagents useful for treatment or prevention of disease or for diagnostic or prognostic methods, including methods in vivo imaging. Such peptides include, for example, growth factors, hormones, cytokines, angiogenic growth factors, extracellular matrix polypeptides, receptor ligands, agonists, antagonists or inverse agonists, peptide

targeting agents, such as imaging agents or cytotoxic  
targeting agents, or polypeptides that exhibit antifusogenic  
and/or antiviral activity, and peptides or polypeptides that  
function as antigens or immunogens including, for example,  
5 viral and bacterial polypeptides.

The invention further relates to methods for enhancing  
the pharmacokinetic properties of any core polypeptide  
through linkage of the core polypeptide to the enhancer  
peptide sequences to form hybrid polypeptides.

10 The invention still further relates to methods for using  
the peptides disclosed herein, including hybrid polypeptides  
containing enhancer peptide sequences. For example, the  
methods of the invention include methods for decreasing or  
inhibiting viral infection, e.g., HIV-1, HIV-2, RSV, measles,  
influenza, parainfluenza, Epstein-Barr, and hepatitis virus  
15 infection, and/or viral-induced cell fusion events. The  
enhancer peptide sequences of the invention can,  
additionally, be utilized to increase the in vitro or ex-vivo  
half-life of a core polypeptide to which enhancer peptide  
sequences have been attached, for example, enhancer peptide  
20 sequences can increase the half life of attached core  
polypeptides in cell culture or cell or tissue samples.

The invention is demonstrated by way of examples wherein  
hybrid polypeptides containing an HIV core polypeptide linked  
to enhancer peptide sequences are shown to exhibit greatly  
enhanced pharmacokinetic properties and act as a potent, non-  
25 cytotoxic inhibitors of HIV-1, HIV-2 and SIV infection. The  
invention is further demonstrated by examples wherein hybrid  
polypeptides containing an RSV core polypeptide or a  
luteinizing hormone polypeptide are shown to exhibit greatly  
enhanced pharmacokinetic properties. In addition, the RSV  
30 hybrid polypeptide exhibited substantial anti-RSV activity.

### 3.2. DEFINITIONS

Peptides, polypeptides and proteins are defined herein as organic compounds comprising two or more amino acids covalently joined, e.g., by peptide amide linkages. Peptides, polypeptide and proteins may also include non-natural amino acids and any of the modifications and additional amino and carboxyl groups as are described herein. The terms "peptide," "polypeptide" and "protein" are, therefore, utilized interchangeably herein.

Peptide sequences defined herein are represented by one-letter symbols for amino acid residues as follows:

A (alanine)  
R (arginine)  
N (asparagine)  
D (aspartic acid)  
C (cysteine)  
Q (glutamine)  
15 E (glutamic acid)  
G (glycine)  
H (histidine)  
I (isoleucine)  
L (leucine)  
K (lysine)  
M (methionine)  
F (phenylalanine)  
20 P (proline)  
S (serine)  
T (threonine)  
W (tryptophan)  
Y (tyrosine)  
V (valine)  
X (any amino acid)

25

"Enhancer peptide sequences" are defined as peptides having the following consensus amino acid sequences:  
"WXXWXXXI", "WXXWXXX", "WXXWXX", "WXXWX", "WXXW", "WXXXWXX",  
"XXXWXX", "XXWXX", "XWXX", "WXW", "WXXWXX", "WXXXWX",  
"WXXXW", "IXXXWXXW", "XXXWXXW", "XXWXXW", "XWXXW",  
30 "XWXXXXW", "XWXXXX", "XWXX", "XWXX", "XW", "WXXXXW",  
or "WXXXW", wherein X can be any amino acid, W represents tryptophan and I represents isoleucine. As discussed below,

the enhancer peptide sequences of the invention also include peptide sequences that are otherwise the same as the consensus amino acid sequences but contain amino acid substitutions, insertions or deletions but which do not abolish the ability of the peptide to enhance the pharmacokinetic properties of a core peptide to which it is linked relative to the pharmacokinetic properties of the core polypeptide alone.

"Core polypeptide" as used herein, refers to any polypeptide which may be introduced into a living system and, thus, represents a bioactive molecule, for example any polypeptide that can function as a pharmacologically useful peptide for treatment or prevention of disease.

"Hybrid polypeptide" as used herein, refers to any polypeptide comprising an amino, carboxy, or amino and carboxy terminal enhancer peptide sequence and a core polypeptide. Typically, an enhancer peptide sequence is linked directly to a core polypeptide. It is to be understood that an enhancer peptide can also be attached to an intervening amino acid sequence present between the enhancer peptide sequence and the core peptide.

"Antifusogenic" and "anti-membrane fusion," as used herein, refer to a peptide's ability to inhibit or reduce the level of fusion events between two or more structures e.g., cell membranes or viral envelopes or pili, relative to the level of membrane fusion which occurs between the structures in the absence of the peptide.

"Antiviral," as used herein, refers to the peptide's ability to inhibit viral infection of cells via, e.g., cell fusion or free virus infection. Such infection can involve membrane fusion, as occurs in the case of enveloped viruses, or another fusion event involving a viral structure and a cellular structure, e.g., fusion of a viral pilus and bacterial membrane during bacterial conjugation).

#### 4. BRIEF DESCRIPTION OF DRAWINGS

FIG. 1. Hybrid polypeptides. Enhancer peptide sequences derived from putative N-terminal and C-terminal interactive regions are depicted linked to a generic core polypeptide. Conserved enhancer peptide sequences are shaded. It is to be noted that the enhancer peptide sequences indicated may be used either as N-terminal, C-terminal, or N- and C-terminal additions. Further, the enhancer peptide sequences can be added to a core polypeptide in forward or reverse orientation, individually or in any of the possible combinations, to enhance pharmacokinetic properties of the peptide.

FIG. 2A. Enhancer peptide sequences derived from various envelope (gp41) protein sequences, representing the N-terminal interactive region observed in all currently published isolate sequences of HIV-1, HIV-2 and SIV. The final sequence "WXXWXXXI" represents a consensus sequence.

FIG. 2B. Enhancer peptide sequence variants derived from various envelope (gp41) protein sequences, representing the C-terminal interactive region observed in all currently published isolate sequences of HIV-1, HIV-2 and SIV. The final sequence "WXXXWXXW" represents a consensus sequence.

FIG. 3. Comparison of HIV-1 titres in tissues of HIV-1 9320 infected SCID-HuPBMC mice as measured by P24 Levels in HuPBMC co-culture assays. The figure shows a comparison of in vivo T20 and T1249 viral inhibition.

FIG. 4A-4B. Plasma pharmacokinetic profile of T1249 vs. T1387 core control in CD-rats following IV injection for up to 2 hrs (FIG. 4A) and 8 hrs (FIG. 4B). The T1387

polypeptide is a core polypeptide and the T1249 polypeptide is the core polypeptide linked to enhancer peptide sequences.

FIG. 5. Plasma pharmacokinetic profile of T1249 vs. T20 control in CD-rats following IV administration. The T1249 polypeptide is a hybrid polypeptide of a core polypeptide (T1387) linked to enhancer peptide sequences. T20: n=4; T1249: n=3.

FIG. 6. Comparison of T20/T1249 Anti-HIV-1/IIIB activity and cytotoxicity.

FIG. 7. Direct Binding of T1249 to gp41 construct M41Δ178. <sup>125</sup>I-T1249 was HPLC purified to maximum specific activity. Saturation binding to M41Δ178 (a gp41 ectodomain fusion protein lacking the T20 amino acid sequence) immobilized in microtitre plates at 0.5 mg/ml is shown.

FIG. 8. Time Course of T1249 Association/Dissociation. The results demonstrate that <sup>125</sup>I-T1249 and <sup>125</sup>I-T20 have similar binding affinities of 1-2 nM. Initial on and off rates for <sup>125</sup>I-T1249 were significantly slower than those of <sup>125</sup>I-T20. Dissociation of bound radioligand was measured following the addition of unlabeled peptide to a final concentration of 10 μM in 1/10 total assay volume.

FIG. 9. Competition for T1249 Binding to M41Δ178. Unlabeled T1249 and T20 were titrated in the presence of a single concentration of either <sup>125</sup>I-T1249 or <sup>125</sup>I-T20. Ligand was added just after the unlabeled peptide to start the incubation.

FIG. 10A-10B. Plasma pharmacokinetic profile of RSV hybrid polypeptides T1301 (10A) and T1302 (10B) vs. T786 in CD rats.

5 FIG. 11A. Plaque Reduction Assay. Hybrid polypeptide T1293 is capable of inhibiting RSV infection with an  $IC_{50}$  2.6  $\mu$ g/ml.

FIG. 11B. Plaque Reduction Assay demonstrates the ability of RSV Hybrid Polypeptides T1301, T1302 and T1303 to  
10 inhibit RSV infection.

FIG. 12A and 12B. Plasma pharmacokinetic profile of luteinizing hormone hybrid polypeptide T1324 vs T1323 in CD male rats. The T1323 polypeptide is a luteinizing hormone  
15 core polypeptide and the T1324 polypeptide is a hybrid polypeptide comprising a core polypeptide linked to enhancer peptide sequences.

FIG. 13. Hybrid polypeptide sequences derived from  
20 various core polypeptides. Core polypeptide sequences are shown shaded. The non-shaded amino and carboxy terminal sequences represent enhancer peptide sequences.

FIG. 14A-B. Circular Dichroism (CD) spectra for T1249 in solution (phosphate buffered saline, pH 7) alone (10  $\mu$ M at  
25 1°C; FIG. 14A) and in combination with a 45-residue peptide from the gp41 HR1 binding domain (T1346); the closed square (■) represents a theoretical CD spectrum predicted for a "non-interaction model" whereas the actual CD spectra are represented by the closed circle (•).

30

FIG. 15. Polyacrylamide gel electrophoresis showing T1249 protection of the gp41 construct M41 $\Delta$ 178 from

proteainase-K digestion; lane 1: primer marker; lane 2: untreated M41Δ178; lane 3: M41Δ178 incubated with proteainase-K; lane 4: untreated T1249; lane 5: T1249 incubated with proteainase-K; lane 6: M41Δ178 incubated with T1249; lane 7: incubation of T1249 and M41Δ178 prior to addition of proteainase-K.

FIG. 16A-C. Pharmacokinetics of T1249 in Sprague-Dawley albino rats; FIG. 16A: pharmacokinetics of T1249 in a single dose administration by continuous subcutaneous infusion; FIG. 16B: Plasma pharmacokinetics of T1249 administered by subcutaneous injection (SC) or intravenous injection (IV); FIG. 16C: Kinetic analysis of T1249 in lymph and plasma after intravenous administration.

FIG. 17A-B Pharmacokinetics of T1249 in cynomolgus monkeys; FIG. 17A: plasma pharmacokinetics of a single 0.8 mg/kg dose of T1249 via subcutaneous (SC) intravenous (IV) or intramuscular (IM) injection; FIG. 17B: Plasma pharmacokinetics of subcutaneously administered T1249 at three different dose levels (0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg).

FIG. 18A-18D. Antiviral activity exhibited by the peptides DP397 (—□—), T649 (—○—) and T1249 (—Δ—) in various T649 resistant strains of HIV-1, as assayed in a Magi-CCR-5 infectivity assay; solid (upper) and dashed (lower) horizontal lines in each figure indicated levels of 50% and 90% reduction in HIV-1 infection, respectively; FIG. 18A: antiviral activity exhibited by DP397, T649 and T1249 in the HIV-1 strain RF-649; FIG. 18B: antiviral activity exhibited by DP397, T649 and T1249 in the HIV-1 strain DH012-649; FIG. 18C: antiviral activity exhibited by DP397, T649 and T1249 in the HIV-1 strain 3'ETVQQQ; FIG. 18D: antiviral

activity exhibited by DP397, T649 and T1249 in the HIV-1 strain SIM-649.

#### 5. DETAILED DESCRIPTION OF THE INVENTION

5 Described herein are peptide sequences, referred to as enhancer peptide sequences, derived from various retroviral envelope (gp41) protein sequences that are capable of enhancing the pharmacokinetic properties of core polypeptides to which they are linked. Such enhancer peptide sequences can be utilized in methods for enhancing the pharmacokinetic  
10 properties of any core polypeptide through linkage of the enhancer peptide sequences to the core polypeptide to form a hybrid polypeptide with enhanced pharmacokinetic properties relative to the core polypeptide alone. The half life of a core peptide to which an enhancer peptide sequence or

15 sequences has been attached can also be increased in vitro. For example, attached enhancer peptide sequences can increase the half life of a core polypeptide when present in cell culture, tissue culture or patient samples, such as cell, tissue, or other samples.

20 The core polypeptides of the hybrid polypeptides of the invention comprise any peptide which may be introduced into a living system, for example, any peptide that can function as a therapeutic or prophylactic reagent useful for treatment or prevention of disease, or an imaging agent useful for imaging structures in vivo.

25 Also described herein are peptides, including peptides that contain enhancer peptide sequences, that exhibit anti-fusogenic and/or anti-viral activity. Further described herein are methods for utilizing such peptides, including methods for decreasing or inhibiting viral infection and/or  
30 viral induced cell fusion.

### 5.1. HYBRID POLYPEPTIDES

The hybrid polypeptides of the invention comprise at least one enhancer peptide sequence and a core polypeptide. Preferably, the hybrid polypeptides of the invention comprise  
5 at least two enhancer peptide sequences and a core polypeptide, with at least one enhancer peptide present in the hybrid polypeptide amino to the core polypeptide and at least one enhancer peptide sequence present in the hybrid polypeptide carboxy to the core polypeptide.

10 The enhancer peptide sequences of the invention comprise peptide sequences originally derived from various retroviral envelope (gp 41) protein sequences, including HIV-1, HIV-2 and SIV sequences, and specific variations or modifications thereof described below. A core polypeptide can comprise any peptide sequence, preferably any peptide sequence that may be  
15 introduced into a living system, including, for example, peptides to be utilized for therapeutic, prophylactic or imaging purposes.

Typically, a hybrid polypeptide will range in length from about 10 to about 500 amino acid residues, with about 10  
20 to about 100 amino acid residues in length being preferred, and about 10 to about 40 amino acids in length being most preferred.

While not wishing to be bound by any particular theory, the structure of the envelope protein is such that the putative  $\alpha$ -helix region located in the C-terminal region of  
25 the protein is believed to associate with the leucine zipper region located in the N-terminal region of the protein. Alignment of the N-terminal and C-terminal enhancer peptide sequence gp41 regions observed in all currently published isolate sequences of HIV-1, HIV-2 and SIV identified  
30 consensus amino acid sequences.

In particular, the following consensus amino acid sequences representing consensus enhancer peptide sequences

were identified (the consensus sequences are listed below in forward and reverse orientations because said enhancer peptide sequences can be utilized either in forward or reverse orientation): "WXXWXXXI", "WXXWXXX", "WXXWXX",  
5 "WXXWX", "WXXW", "WXXXWXWX", "XXXWXWX", "XXWXWX", "XWXWX",  
"WXXW", "WXXXWXW", "WXXXWX", "WXXXW", "IXXXWXXW", "XXXWXXW",  
"XXWXXW", "XWXXW", "XWXWXXXW", "XWXWXXX", "XWXWXX", "XWXWX",  
"XWXW", "WXWXXXW", or "XWXXXW", wherein X can be any amino acid, W represents tryptophan and I represents isoleucine.  
Forward orientations of consensus amino acid sequences are  
10 shown in FIGS. 1 and 2.

Typically, an enhancer peptide sequence will be about 4,  
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,  
21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 amino acid residues  
in length, with about 4 to about 20 residues in length being  
15 preferred, about 4 to about 10 residues in length being more  
preferred, and about 6 to about 8 residues in length being  
most preferred.

In a preferred embodiment of the invention, enhancer  
peptide sequences which may be used to enhance the  
20 pharmacokinetic properties of the resultant hybrid  
polypeptides comprise the specific enhancer peptide sequences  
depicted in FIGS. 2, 13, and Table 1, below. Among the most  
preferred enhancer peptide sequences are ones comprising the  
following amino sequence: "WQEWEQKI" and "WASLWEWF".

By way of example and not by way of limitation, Table 1,  
25 below, lists amino acid sequences that represent preferred  
embodiments of the enhancer peptide sequences of the enhancer  
peptide sequences of the invention. It is to be understood  
that while the forward orientation of these sequences is  
depicted below, the reverse orientation of the sequences is  
30 also intended to fall within the scope of the present  
invention. For example, while the forward orientation of the  
enhancer peptide sequence "WMEWDREI" is depicted below, its

reverse orientation, i.e., "IERDWEMW" is also intended to be included.

TABLE 1

5	WMEWDREI
	WQEWERKV
	WQEWQKV
	MTWMEWDREI
10	NNMTWMEWDREI
	WQEWQKVRYLEANI
	NNMTWQEWZKVRYLEANI
	WNWFI
	WQEWDREISNYTSLI
	WQEWEREISAYTSLI
15	WQEWDREI
	WQEWFI
	WNWF
	WQEW
	WQAW
20	WQEWQKI
	WASLWNWF
	WASLFNFF
	WDVFTNWL
	WASLWEWF
25	EWASLWEWF
	WEWF
	EWEIF
	IEWEIF
	IEWEIF
	EWEIF
30	WASLWEWF
	WAGLWEWF
	AKWASLWEWF

5 AEWASLWEWF  
WASLWAWF  
AEWASLWAWF  
AKWASLWAWF  
WAGLWAWF  
AEWAGLWAWF  
WASLWAW  
AEWASLWAW  
WAGLWAW  
10 AEWAGLWAW  
DKWEWF  
IEWASLWEWF  
IKWASLWEWF  
DEWEWF  
GGWASLWNWF  
15 GGWNWF

In another preferred embodiment, particular enhancer peptide sequences of the invention comprise the enhancer peptide sequences depicted in FIGS. 2, 13 and Table 1  
20 exhibiting conservative amino acid substitutions at one, two or three positions, wherein said substitutions do not abolish the ability of the enhancer peptide sequence to enhance the pharmacokinetic properties of a hybrid polypeptide relative to its corresponding core polypeptide.

Most preferably, such substitutions result in enhancer  
25 peptide sequences that fall within one of the enhancer peptide sequence consensus sequences. As such, generally, the substitutions are made at amino acid residues corresponding to the "X" positions depicted in the consensus amino acid sequences depicted above and in FIGS. 1 and 2.  
30 "Conservative substitutions" refer to substitutions with amino acid residues of similar charge, size and/or hydrophobicity/hydrophilicity characteristics as the amino

acid residue being substituted. Such amino acid characteristics are well known to those of skill in the art.

The present invention further provides enhancer peptide sequences comprising amino acid sequences of FIGS. 1, 2, 13 and Table 1 that are otherwise the same, but, that said enhancer peptide sequences comprise one or more amino acid additions (generally no greater than about 15 amino acid residues in length), deletions (for example, amino- or terminal- truncations) or non-conservative substitutions which nevertheless do not abolish the resulting enhancer peptide's ability to increase the pharmacokinetic properties of core polypeptides to which they are linked relative to core polypeptides without such enhancer peptide sequences.

Additions are generally no greater than about 15 amino acid residues and can include additions of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 consecutive amino acid residues. Preferably the total number of amino acid residues added to the original enhancer peptide is no greater than about 15 amino acid residues, more preferably no greater than about ten amino acid residues and most preferably no greater than about 5 amino acid residues.

Deletions are preferably deletions of no greater than about 3 amino acid residues in total (either consecutive or non-consecutive residues), more deletions preferably of 2 amino acids, most preferably deletions of single amino acids residues. Generally, deletions will be of amino acid residues corresponding to the "X" residues of the enhancer peptide consensus sequences.

Enhancer peptide sequences of the invention also comprise the particular enhancer peptide sequences depicted in FIGS. 2, 13 and Table 1 exhibiting one, two or three non-conservative amino acid substitutions, with two such substitutions being preferred and one such substitution being most preferred. "Non conservative" substitutions refer to

substitutions with amino acid residues of dissimilar charge, size, and/or hydrophobicity/ hydrophilicity characteristics from the amino acid residue being replaced. Such amino acid characteristics are well known to those of skill in the art.

- 5 In addition, the amino acid substitutions need not be, and in certain embodiments preferably are not, restricted to the genetically encoded amino acids. Indeed, the peptides may contain genetically non-encoded amino acids. Thus, in addition to the naturally occurring genetically encoded amino acids, amino acid residues in the peptides may be substituted  
10 with naturally occurring non-encoded amino acids and synthetic amino acids. Such substitutions can also be present within the core polypeptides of the hybrid polypeptides of the invention, whether or not they are present in the enhancer sequence/sequences of the particular  
15 hybrid polypeptide.

- Certain commonly encountered amino acids which provide useful substitutions include, but are not limited to,  $\beta$ -alanine ( $\beta$ -Ala) and other omega-amino acids such as 3-aminopropionic acid, 2,3-diaminopropionic acid (Dpr),  
20 4-aminobutyric acid and so forth;  $\alpha$ -aminoisobutyric acid (Aib);  $\epsilon$ -aminohexanoic acid (Aha);  $\delta$ -aminovaleric acid (Ava); N-methylglycine or sarcosine (MeGly); ornithine (Orn); citrulline (Cit); t-butylalanine (t-BuA); t-butylglycine (t-BuG); N-methylisoleucine (MeIle); phenylglycine (Phg); cyclohexylalanine (Cha); norleucine (Nle); naphthylalanine  
25 (Nal); 4-chlorophenylalanine (Phe(4-Cl)); 2-fluorophenylalanine (Phe(2-F)); 3-fluorophenylalanine (Phe(3-F)); 4-fluorophenylalanine (Phe(4-F)); penicillamine (Pen); 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic);  $\beta$ -2-thienylalanine (Thi); methionine sulfoxide (MSO);  
30 homoarginine (hArg); N-acetyl lysine (AcLys); 2,4-diaminobutyric acid (Dbu); 2,3-diaminobutyric acid (Dab); p-aminophenylalanine (Phe(pNH<sub>2</sub>)); N-methyl valine (MeVal);

homocysteine (hCys), homophenylalanine (hPhe) and homoserine (hSer); hydroxyproline (Hyp), homoproline (hPro), -methylated amino acids, cyclic amino acid analogues (used, e.g., to constrain amino acid residues to particular conformational states, e.g.,  $\alpha$   $\alpha'$ - and  $\beta\beta'$ -substituted cyclic amino acids such as 1-aminocyclopentanecarboxylic acid (cycloleucine) and  $\beta,\beta$ -cyclopentamethylene- $\beta$ -mercaptopropionic acid (see, e.g., Hruby et al., 1990, Biochem. J. 268:249-262). and peptoids or oligopeptoids (N-substituted amino acids, e.g., N-substituted glycines; see, e.g., Simon et al., 1972, Proc. Natl. Acad. Sci. USA 89:9367-9371).

While in most instances, the amino acids of the peptide will be substituted with L-enantiomeric amino acids, the substitutions are not limited to L-enantiomeric amino acids. Thus, also included in the definition of "mutated" or "altered" forms are those situations where an L-amino acid is replaced with an identical D-amino acid (e.g., L-Arg - D-Arg) or with a D-amino acid of the same category or subcategory (e.g., L-Arg - D-Lys), and vice versa. Such substitutions can also be present within the core polypeptides of the hybrid polypeptides of the invention, whether or not they are present in the enhancer sequence/sequences of the particular hybrid polypeptide.

In addition to the above-described amino acid substitutions, replacement of side chain moieties can be made by introducing, for example, a methyl group or pseudoisosteric groups with different electronic properties (see, e.g., Hruby et al., 1990, Biochem. J. 268:249-262). Further, double bonds can be introduced between adjacent carbon atoms of amino acids and cyclic peptides or analogs can be formed by introducing covalent bonds such as forming an amide bond between - and C- termini, between two side chains or between a side chain and the - or

C- terminus of the peptide. Such substitutions can also be present within the core polypeptides of the hybrid polypeptides of the invention, whether or not they are present in the enhancer sequence/sequences of the particular  
5 hybrid polypeptide.

The core and hybrid polypeptides of the invention can also be conjugated with one or more chemical groups. The chemical groups utilized for conjugation are preferably not significantly toxic or immunogenic, i.e., any toxicity or immunogenicity observed with a conjugate of a core or hybrid  
10 polypeptide is not significantly (i.e., less than 50%) greater than any toxicity or immunogenicity observed with the corresponding unmodified core or hybrid polypeptide. Chemical modifications of the core and/or hybrid polypeptides are intended to affect the pharmacokinetic properties of the  
15 polypeptide. These effects include a decrease or increase in drug potency, stability, bioactivity, clearance, immunogenicity, and in vivo half-life, as well as effects on the polypeptide's catabolization, trafficking and localization.

20 In one embodiment, hybrid polypeptides are conjugated with one or more chemical groups at both the core and enhancer polypeptide portions. In another embodiment, such modifications are made either to the core polypeptide or the enhancer peptide portions of the hybrid polypeptides. In yet another embodiment, only the core polypeptide portion of the  
25 hybrid polypeptide is modified. In still another embodiment, the core polypeptide is modified by one or more chemical groups, where such core polypeptide is not present as part of a hybrid polypeptide. For example, a core polypeptide such as T1387 (Ac-TALLEQAQIQQEKNEYELQKLDK-NH<sub>2</sub>) can be modified  
30 utilizing one or more chemical groups.

Exemplary chemical groups useful for conjugation include non-proteinaceous polymers, such as polyols. Other chemical

groups include proteins, such as, for example, albumin or immunoglobulin, as well as carbohydrates, such as, for example, those carbohydrates that occur naturally on glycoproteins. Dextran, DL-amino acids, and polyvinyl pyrrolidone have also been used to modify proteins. For a review of polymer-modified peptides, see e.g., Burnham, *Am. J. Hosp. Pharm.* 51:210-18 (1994), which is incorporated herein by reference in its entirety.

A polyol, for example, can be conjugated to a core or hybrid polypeptide at one or more amino acid residues, including, for example, lysine, cysteine and histidine residues. The polyol employed can be any water-soluble poly(alkylene oxide) polymer and can have a linear or branched chain. Suitable polyols include those substituted at one or more hydroxyl positions with a chemical group, such as an alkyl group having between one and four carbons. Typically, the polyol is a poly(alkylene glycol), such as poly(ethylene glycol) (PEG), and thus, for ease of description, the remainder of the discussion relates to an exemplary embodiment wherein the polyol employed is PEG and the process of conjugating the polyol to a core or hybrid polypeptide is termed "pegylation." However, those skilled in the art recognize that other polyols, such as, for example, poly(propylene glycol) and polyethylene-polypropylene glycol copolymers, can be employed using the techniques for conjugation described herein for PEG. For a review of modification of bioactive molecules by PEG or its derivatives, see e.g., Inada et al., *Trends Biotechnol.* 13:86-91 (1995), which is incorporated herein by reference in its entirety.

The degree of pegylation of a core or hybrid polypeptide of the present invention can be adjusted to provide a desirably increased half-life in vivo, compared to the corresponding non-pegylated protein. The half-life of a

pegylated core or hybrid polypeptide can increase incrementally with increasing degrees of pegylation. Modification of proteins with PEG or PEG derivatives has been demonstrated to increase desirably drug potency, bioactivity, stability (including resistance against heat, chemical denaturants, and proteolysis), *in vivo* absorption/uptake, and *in vivo* half-life, as well as desirably reduce clearance rates and immunogenicity (U.S. Patent No. 6,025,325; Westerman et al., *Int. J. Cancer* 76:842-50 (1998); Conover et al., *Artif. Organs* 21:907-15 (1997); Tsutsumi et al., *J. Pharmacol. Exp. Ther.* 278:1006-11 (1996); Kaneda et al., *Invasion Metastasis* 15:156-62 (1995); Inada et al., *Trends Biotechnol.* 13:86-91 (1995); Paige et al., *Pharm. Res.* 12:1883-88 (1995); Satake-Ishikawa et al., *Cell Struct. Funct.* 17:157-60 (1992); Tanaka et al., *Cancer Res.* 51:3710-3714 (1991), which are incorporated herein by reference in its entirety).

The average molecular weight of the PEG can range from about 500 to about 30,000 daltons (D); preferably, from about 1,000 to about 25,000 D; and more preferably, from about 4,000 to about 20,000 D. In one embodiment, pegylation is carried out with PEG having an average molecular weight of about 5,000 D (hereinafter "PEG(5000)"). In another embodiment, a branched-chain PEG having two chains of about 10,000 D each is employed.

PEG preparations that are commercially available, and suitable for use in the present invention, are nonhomogeneous preparations that are sold according to average molecular weight. For example, PEG(5000) preparations typically contain molecules that vary slightly in molecular weight, usually +/-500 D. A variety of methods for pegylation of proteins have been described. See, e.g., U.S. Patent No. 4,179,337, which is incorporated herein by reference in its entirety, disclosing the conjugation of a number of hormones

and enzymes to PEG and polypropylene glycol to produce physiologically active non-immunogenic compositions.

Reaction conditions for coupling PEG to a protein vary depending on the target protein, the desired degree of  
5 pegylation, the PEG type or derivative used, and the target point of attachment. Other considerations include the stability, reactivity, and antigenicity of the PEG linkage. Generally, a PEG having at least one terminal hydroxy group is reacted with a coupling agent to form an activated PEG  
10 having a terminal reactive group. Id. This reactive group then reacts with the  $\alpha$ - and  $\epsilon$ -amines of proteins to form a covalent bond. Amine groups can conjugate with the hydroxy group of a PEG to form an amide linkage. Carboxy groups can conjugate with the amine groups of the core or hybrid polypeptide to form an amide bond and with the hydroxy group  
15 of a PEG to form an ester. Conveniently, the other end of the PEG molecule can be "blocked" with a non-reactive chemical group, as a methoxy group to produce, for example, alkylated PEGs such as methoxy-PEG (MPEG), which reduces the formation of PEG-crosslinked complexes of protein molecules.

Several types of linker groups known in the art can be  
20 employed to conjugate a core, enhancer or hybrid polypeptide to a PEG. For examples of linking groups, see e.g., U.S. Patent No. 4,609,546; U.S. Patent No. 4,847,325; U.S. Patent No. 4,902,502; U.S. Patent No. 5,034,514; and U.S. Patent No.  
25 5,122,614. In one embodiment, an enhancer peptide sequence is employed as a linker.

Suitable activated PEGs can be produced by a number of conventional reactions. For example, an N-hydroxysuccinimide ester of a PEG (M-NHS-PEG) can be prepared from  
PEG-monomethyl ether (which is commercially available from  
30 Union Carbide) by reaction with N,N'-dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide (NHS), according to the method of Buckmann and Merr, *Makromol. Chem.*, 182:1379-1384 (1981).

In addition, a PEG terminal hydroxy group can be converted to an amino group, for example, by reaction with thionyl bromide to form PEG-Br, followed by aminolysis with excess ammonia to form PEG-NH<sub>2</sub>. The PEG-NH<sub>2</sub> is then  
5 conjugated to the protein of interest using standard coupling reagents, such as Woodward's Reagent K. Furthermore, a PEG-terminal -CH<sub>2</sub>OH group can be converted to an aldehyde group, for example, by oxidation with MnO<sub>2</sub>. The aldehyde group is conjugated to the protein by reductive alkylation with a reagent such as cyanoborohydride. Amino acids also can be  
10 coupled to PEG through their amine groups via an appropriate linkage, such as, for example a urethane group. An unnatural amino acid, norleucine, can be activated at its carboxylic group to succinimidyl ester for binding to the amino groups of a protein (Zalipsky et al., *Int. J. Peptide Protein Res.*  
15 30:740 (1987); Sartore et al., *Appl. Biochem. Biotech.* 27:45 (1991)). For a general review of pegylation, see e.g. Zalipsky and Lee in "Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications," J. M. Harris, Ed., Plenum, NY, Chap. 21 (1992), which is incorporated herein by  
20 reference in its entirety.

Alternatively, activated PEGs suitable for use in the present invention, such as, but not limited to, acrylate PEG, aldehyde PEG, allyl PEG, amino PEG, amino acid PEG, amino acid esters of PEG,  $\omega$ -amino  $\alpha$ -carboxyl PEG, benzotriazole  
25 carbonate, biotin PEG, t-Boc PEG, carbonylimidazole PEG, carboxymethylated PEG, epoxide PEG, Fmoc PEG, fluorescein PEG, hydrazide PEG,  $\omega$ -hydroxy  $\alpha$ -amino PEG,  $\omega$ -hydroxy  $\alpha$ -carboxyl PEG, isocyanate PEG, maleimide PEG, methacrylate ester of PEG, NHS-maleimide, NHS-vinylsulfone,  
30 p-nitrophenylcarbonate PEG, orthopyridyl disulfide, PEG<sub>2</sub>, phospholipid PEG, propionic acid PEG, silane PEG, succinate PEG, succinimidyl butanoate PEG (SBA-PEG), succinimidyl ester

of amino acid PEG, succinimidyl ester of carboxymethylated PEG, succinimidyl propionate PEG (SPA-PEG), succinimidyl succinate PEG (SS-PEG), thiol PEG, vinylsulfone PEG, can be purchased from a number of vendors. For example, Shearwater  
5 Polymers, Inc. (Huntsville, Ala.) sells M-NHS-PEG as "SCM-PEG" in addition to a succinimidyl carbonate of MPEG ("SC-PEG") and MPEG succinimidyl propionate ("SPA-PEG").

Particular amino acids comprising the hybrid or core polypeptide can be modified, for example, to prevent and/or facilitate pegylation of certain amino acid residues. In one  
10 embodiment, potential pegylation sites can be inactivated by modification of amino acid residues that can be pegylated. For example, all amino acid residues possessing a free amino group in a core or hybrid polypeptide can be protected, thereby preventing pegylation at those residues. Suitable  
15 protecting groups include, but are not limited to, tert-butoxycarbonyl (t-Boc) and N-9-fluorenylmethyloxy carbonyl (Fmoc). Any amine protecting group suitable for peptide synthesis can be used. Several such protecting groups are described in Greene, Protective Groups in Organic  
20 Synthesis, John Wiley & Sons, New York, 1981, pp. 323-334; and Fields and Noble, *Int. J. Pept. Protein Res.* 35:161-214 (1990), which are incorporated herein by reference in its entirety. If desired, the protecting group subsequently can be removed by routine chemistry, e.g., treatment with  
25 piperidine in dimethylformamide in the case of Fmoc, or treatment with trifluoroacetic acid in the case of t-Boc.

Alternatively, amino acid residues of the core or hybrid polypeptide that are susceptible to pegylation can be replaced, for example, by site-directed mutagenesis, with an amino acid residue resistant to pegylation. Moreover,  
30 enhancer peptide sequences, lacking amino acid residues that are susceptible to pegylation, can be used to generate hybrid polypeptides.

In another embodiment, one or more amino acid residues of the core or hybrid polypeptide can be modified so as to introduce additional pegylation sites. For example, one or more amino acid residues that are susceptible to pegylation  
5 can be replaced or added to the polypeptide by any method known in the art, such as by standard synthesis techniques or, in the case of recombinant techniques, via site-directed mutagenesis (Zoller et al., *Nucl. Acids Res.* 10:6487 (1987); Carter et al., *Nucl. Acids Res.* 13:4331 (1986)).

10 Pegylation of the core or hybrid polypeptide can also be manipulated to direct the site of attachment or affect the degree of pegylation. Pegylation only of a portion of the possible pegylation sites of a core or hybrid polypeptide can be accomplished by any method known in the art. For example, the degree of pegylation can be controlled by the reaction  
15 conditions, such as by adjusting the molar ratio of polypeptide to PEG, duration of the reaction, or temperature at which the reaction is done. After purification of the pegylated polypeptide by, for example, ion exchange chromatography, the degree of pegylation can be assessed by,  
20 for example, SDS-PAGE analysis. The pegylated protein can be stored using any storage medium described in the art, including storage at -20°C in PBS buffer (pH 7.3).

These approaches can be combined to control the number and location of pegylation sites along the core or hybrid  
25 polypeptide. Pegylation of a particular amino acid residue of interest can be accomplished by combining chemical protection techniques and pegylation reactions during synthesis of the core, enhancer, or hybrid polypeptides. Use of different protecting groups combined with protection or deprotection at different points during peptide synthesis  
30 will allow targeting of any amino acid residue(s) for pegylation. Thus, this technique can be employed to modify selectively, with any chemical group, any portion of, or

specific amino acid residue within a core, enhancer, or hybrid polypeptide. For example, a partially synthesized oligopeptide can be chemically protected using a first protecting group to prevent pegylation of amino acid residues that would otherwise be susceptible to pegylation. Synthesis  
5 of the polypeptide can then be completed, using a second protecting group that would also protect amino acid residues that would otherwise be susceptible to pegylation. The second protecting group should be more labile than the first, such that upon completion of synthesis, the labile protecting  
10 group can be selectively removed, allowing pegylation of only the now unprotected amino acid residues of interest (Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1981).

In one non-limiting example, any one of the amino acid  
15 residues of T1387 (Ac-TALLEQAQIQQEKNEYELQKLDK-NH<sub>2</sub>) that is susceptible to pegylation (e.g., lysine residues) can be selectively modified. For example, KLDK can be synthesized, and the  $\epsilon$ -NH<sub>2</sub> group of the lysine residues can be deprotected and pegylated. Peptide synthesis then would be completed to  
20 yield a core polypeptide, which has only two of the three lysine residues pegylated.

In another non-limiting example, the most N-terminal lysine residue of T1387 can be modified by synthesizing NEYELQKLDK, and protecting the  $\epsilon$ -NH<sub>2</sub> groups of the lysine  
25 residues with a less labile protecting group. After completion of protein synthesis, in which the  $\epsilon$ -NH<sub>2</sub> group of the most N-terminal lysine has a more labile protecting group, the N-terminal lysine is then selectively deprotected and pegylated. It should be clear to those skilled in the  
30 art that strategies such as these can be used to selectively modify any target amino acid residue(s) within a core, enhancer, or hybrid polypeptide. Such protecting groups and

their labilities can be found in the art, such as Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1981.

One or more additional amino acid sequences also can be conjugated to core or hybrid polypeptides. The amino acid sequence employed can be any amino acid sequence that demonstrates a long half-life, or may do so in context of a fusion protein. In one embodiment, the protein utilized is of human origin. In a preferred embodiment, the protein is human albumin. However, those skilled in the art recognize that other proteins, such as, for example, immunoglobulins, can be employed using the techniques for conjugation described herein for albumin. For example, a core, enhancer, or hybrid polypeptide can be conjugated with a member of the immunoglobulin family or fragments of immunoglobulins. In one embodiment, a core, enhancer, or hybrid polypeptide is fused to the human IgG1 Fc domain.

In another embodiment, the polypeptide is modified by attachment of both a non-proteinaceous polyol modification and an amino acid sequence modification, such as modifications using both PEG and albumin.

Amino acid sequences can be attached either to the C-terminal or N-terminal ends of the core, enhancer, or hybrid polypeptide or attached as side-chains along the polypeptide. Amino acid sequences may be added to the core or hybrid polypeptide either during or after polypeptide synthesis. Alternatively, a construct can be designed to produce a fusion protein such that the recombinant amino acid sequence is attached to the core and/or hybrid polypeptide. For example, albumin can be fused to either end of the core polypeptide. If desired, enhancer peptide sequences can then be placed at the free end of the core polypeptide and/or at the end of the attached recombinant protein. In one

embodiment, the amino acid sequences can be part of, or can serve as, a linker between core and enhancer polypeptides.

Modification of proteins by fusion with amino acid sequences, such as albumin, has been shown to increase  
5 desirably drug potency, stability, bioactivity, and *in vivo* half-life, as well as desirably reduce clearance and toxicity (Kratz et al., *Arch. Pharm. (Weinheim)* 331:47-53 (1998); Syed et al., *Blood* 89:3243-3252 (1997); Makrides et al., *J. Pharmacol. Exp. Ther.* 277:534-42 (1996); Breton et al., *Eur. J. Biochem.* 231:563-69 (1995); Paige et al., *Pharm. Res.*  
10 12:1883-88 (1995)).

Albumin is highly polymorphic such that many variants have been identified (Weitkamp et al., *Ann. Hum. Genet.* 37:219 (1973)). Albumin sequences, for example human albumin sequences, are well known to those of skill in the art (see,  
15 e.g., U.S. Patent No. 5,876,969, which is incorporated herein by reference in its entirety). Albumin sequences that can be utilized for such protein modifications can include, for example, pre-pro forms, full-length forms, or fragments thereof (see, e.g., Kratz et al., *Arch. Pharm. (Weinheim)*  
20 331:47-53 (1998); Syed et al., *Blood* 89:3243-3252 (1997); Makrides et al., *J. Pharmacol. Exp. Ther.* 277:534-42 (1996); Breton et al., *Eur. J. Biochem.* 231:563-69 (1995); Paige et al., *Pharm. Res.* 12:1883-88 (1995)). Albumin sequences can be added to the polypeptides of the present invention via  
25 chemical synthesis or recombinant techniques, or a combination thereof.

In one non-limiting example, full-length human albumin can be fused in-frame to T1387 (Ac-TALLEQAQIQQEKNEYELQKLDK-NH<sub>2</sub>) via recombinant techniques.

In another non-limiting example, T1387 (Ac-TALLEQAQIQQEKNEYELQKLDK-NH<sub>2</sub>) that has been pegylated can be  
30 conjugated with reduced human albumin (available from Sigma

Chemical, St. Louis) using techniques known in the art, such as Paige et al., *Pharm. Res.* 12:1883-88 (1995).

The modified polypeptides can be tested for biological activity, e.g., antiviral activity, utilizing standard techniques. Further, such features, for example, as pharmacokinetic or immunogenic attributes of the modified polypeptides, can also be routinely assayed. The modified polypeptides also can be subjected to *in vitro* and *in vivo* testing to determine changes in biological response due to the modification(s).

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TABLE 2

T No.	Sequence
1	GIKQLQARILAVERYLKDQ
2	NNLLRAIEAQQHLLQLTVW
3	NEQELLELDKWASLWNWF
5 4	YTSLIHSLIEESQNQQEK
5	Ac-VWGIKQLQARILAVERYLKDQQLLGIWG-NH2
6	QHLLQLTVWGIKQLQARILAVERYLKDQ
7	LRAIEAQQHLLQLTVWGIKQLQARILAV
8	VQQQNNLLRAIEAQQHLLQLTVWGIKQL
9	RQLLSGIVQQQNNLLRAIEAQQHLLQLT
10 10	MTLTVQARQLLSGIVQQQNNLLRAIEAQ
12	VVSLSNGVSVLTSTKVLDLKNIYIDKQLL
13	LLSTNKAVVSLSNGVSVLTSTKVLDLKNI
15	Ac-VLHLEGEVNIKSALLSTNKAVVSLSNG-NH2
19	Ac-LLSTNKAVVSLSNGVSVLTSTKVLDLKNI-NH2
20	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
21	Ac-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
22	Ac-IELSNIKENKCNGTDAKVLIKQELDKYKNAVTELQLLMQST-NH2
15 23	Ac-IELSNIKENKCNGTDAKVLIKQELDKY-NH2
24	Ac-ENKCNGTDAKVLIKQELDKYKNAVTEL-NH2
25	Ac-DAKVLIKQELDKYKNAVTELQLLMQST-NH2
26	Ac-CNGTDAKVLIKQELDKYKNAVTELQLL-NH2
27	Ac-SNIKENKCNGTDAKVLIKQELDKYKNAVTELQLL-NH2
28	Ac-ASGVAVSKVLHLEGEVNIKSALLSTNKAVVSLSNGV-NH2
29	Ac-SGVAVSKVLHLEGEVNIKSALLSTNKAVVSLSNG-NH2
20 30	Ac-VLHLEGEVNIKSALLSTHKAVVSLSNGVSVLTSTK-NH2
31	Ac-ARKLQRMKQLEDKVEELLSKNYHYLENEVARLKKLV-NH2
32	Ac-RMKQLEDKVEELLSKNYHYLENEVARLKKLVGER-NH2
33	Ac-VQQQNNLLRAIEAQQHLLQLTVWGIKQL-NH2
34	Ac-LRAIEAQQHLLQLTVWGIKQLQARILAV-NH2
35	Ac-QHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
36	Ac-RQLLSGIVQQQNNLLRAIEAQQHLLQLT-NH2
25 37	Ac-MTLTVQARQLLSGIVQQQNNLLRAIEAQ-NH2
38	Ac-AKQARSDIEKLKEAIRDITNKAVQSVQSS-NH2
39	Ac-AAVALVEAKQARSDIEKLKEAIRDITNKAVQSVQSS-NH2
40	Ac-AKQARSDIEKLKEAIRDITNKAVQSVQSSIGNLIVA-NH2
41	Ac-GTIALGVATSAQITAVALVEAKQARSD-NH2
42	Ac-ATSAQITAVALVEAKQARSDIEKLKEA-NH2
43	Ac-AAVALVEAKQARSDIEKLKEAIRDITNKANH2
30 44	Ac-IEKLKEAIRDITNKAVQSVQSSIGNLIVA-NH2
45	Ac-IRDITNKAVQSVQSSIGNLIVAIAKSVQDY-NH2
46	Ac-AVQSVQSSIGNLIVAIAKSVQDYVNKEIV-NH2
47	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLARILAVERYLKDQ-NH2

T	No.	Sequence
	48	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQ-NH2
	49	Ac-MTWEMDREINNYTSLIGSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	50	Ac-WMEWDREINNYTSLIGSLIEESQNQQEKNEQELLE-NH2
	51	Ac-INNYTSLIGSLIEESQNQQEKNEQELLE-NH2
5	52	Ac-INNYTSLIGSLIEESQNQQEKNEQELLELDKWASL-NH2
	53	Ac-EWDREINNYTSLIGSLIEESQNQQEKNEQEGGC-NH2
	54	Ac-QSRTLLAGIVQQQQQLLDVVKRQELLR-NH2
	55	Ac-NNDTWQWERKVDFFLEENITALLEEAIQQEKNMYELQKLNSWD-NH2
	56	Ac-WQWERKVDFFLEENITALLEEAIQQEK-NH2
	57	Ac-VDFLEENITALLEEAIQQEKNMYELQK-NH2
	58	Ac-ITALLEEAIQQEKNMYELQKLNSWDVF-NH2
10	59	Ac-SSESFTLLEQWNNWKLQLAEQWLEQINEKHYLEDIS-NH2
	60	Ac-DKWASLWNWF-NH2
	61	Ac-NEQELLELDKWASLWNWF-NH2
	62	Ac-EKNEQELLELDKWASLWNWF-NH2
	63	Ac-NQQEKNEQELLELDKWASLWNWF-NH2
	64	Ac-ESQNQQEKNEQELLELDKWASLWNWF-NH2
	65	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
15	66	Ac-NDQKKLMSNNVQIVRQQSYSIMSIKEE-NH2
	67	Ac-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
	68	Ac-VSKGYSALRTGWYTSVITIELSNIKEN-NH2
	69	Ac-VVSLSNGVSVLTSTKVLDLKNYIDKQLL-NH2
	70	Ac-VNKKISALLSTNKAVVSLSNGVSVLTSTK-NH2
	71	Ac-PIINFYDPLVFPSEDFDASISQVNEKINQSLAFIR-NH2
	72	Ac-NLVYAQLQFTYDTLRGYINRALAQIAEA-NH2
20	73	Ac-LNQVDLTETTLERYQORLNTYALVSKDASYRS-NH2
	74	Ac-ELLVLKKAQLNRHSYKDSDFLDAALD-NH2
	75	Ac-LAEAGEESVTEDETEREDTEEREDEEEE-NH2
	76	Ac-ALLAEAGEESVTEDETEREDTEEREDEEEENEART-NH2
	77	Ac-ETERSVDLVAALLAEAGEESVTEDETEREDTEERE-NH2
	78	Ac-EESVTEDETEREDTEEREDEEEENEART-NH2
	79	Ac-VDLVAALLAEAGEESVTEDETEREDTEEE-NH2
25	80	Ac-NSETERSVDLVAALLAEAGEESVTE-NH2
	81	Ac-DISYAQLQFTYDVLKDYINDALRNIMDA-NH2
	82	Ac-SNVFSKDEIMREYNSQKQHIRTLSAKVNDN-NH2
	83	Biotin-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	84	Dig-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	85	Biotin-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	86	Dig-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
30	87	Ac-VLHQNLNIQLKQYLETQERLLAGNRIAARQLLQIWKDVA-NH2
	88	Ac-LWHEQLLNTAQRAQLQLINQALAVREKVLIRYDIQK-NH2
	89	Ac-LLDNFESTWEQSKELWEQQEISIQNLHKSALQEYW-NH2
	90	Ac-LSNLLQISNNSDEWLEALEIEHEKWKLTQWQSYEQF-NH2

T	No.	Sequence
	91	Ac-KLEALEGKLEALEGKLEALEGKLEALEGKLEALEGK-NH2
	92	Ac-ELRALRGELRALRGELRALRGELRALRGK-NH2
	93	Ac-ELKAKELEGEGLAEGEALKGLLEKAAKLEGLELLK-NH2
	94	Ac-WEAAAREAAAAREAAAAREAAAARA-NH2
5	95	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNAF-NH2
	96	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLANWF-NH2
	97	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	98	Ac-YTSLIHSLIEESQNQQEKNEQELLQLDKWASLWNWF-NH2
	99	Ac-YTSLIHSLIEESQNQQEKNEQELLQLDKWASLWNWF-NH2
	100	Ac-RMKQLEDKVEELLSKNYHLENEVARLKKLVGER-NH2
	101	Ac-QQLQLTVWGIKQLQARILAVERYLKNQ-NH2
10	102	Ac-NEQELLELDKWASLWNWF-NH2
	103	Ac-YTSLIQSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	104	Ac-IINFYDPLVFPSEFDASISQVNEKINQSLAFIRK-NH2
	105	Ac-INFYDPLVFPSEFDASISQVNEKINQSLAFIRKS-NH2
	106	Ac-NFYDPLVFPSEFDASISQVNEKINQSLAFIRKSD-NH2
	107	Ac-FYDPLVFPSEFDASISQVNEKINQSLAFIRKSDE-NH2
	108	Ac-YDPLVFPSEFDASISQVNEKINQSLAFIRKSDEL-NH2
15	109	Ac-DPLVFPSEFDASISQVNEKINQSLAFIRKSDELL-NH2
	110	Ac-PLVFPSEFDASISQVNEKINQSLAFIRKSDELLH-NH2
	111	Ac-LVFPSEFDASISQVNEKINQSLAFIRKSDELLHN-NH2
	112	Ac-VFPSEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
	113	Ac-FPSEFDASISQVNEKINQSLAFIRKSDELLHNVN-NH2
	114	Ac-PSDEFDASISQVNEKINQSLAFIRKSDELLHNVNA-NH2
	115	Ac-SDEFDASISQVNEKINQSLAFIRKSDELLHNVNAG-NH2
20	116	Ac-DEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
	117	Ac-EFDASISQVNEKINQSLAFIRKSDELLHNVNAGKS-NH2
	118	Ac-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
	119	Ac-DASISQVNEKINQSLAFIRKSDELLHNVNAGKSTT-NH2
	120	Ac-ASGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSN-NH2
	121	Ac-SGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
	122	Ac-GVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGV-NH2
25	123	Ac-VAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVS-NH2
	124	Ac-AVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSV-NH2
	125	Ac-VSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVL-NH2
	126	Ac-SKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLT-NH2
	127	Ac-KVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTS-NH2
	128	Ac-VLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSK-NH2
	129	Ac-LHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKV-NH2
30	130	Ac-HLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVL-NH2
	131	Ac-LEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLD-NH2
	132	Ac-EGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDL-NH2
	133	Ac-GEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLK-NH2

T		No.	Sequence
		134	Ac-EVNKIKSALLSTNKAVVSLNNGVSVLTISKVLDLKN-NH2
		135	Ac-VNKKIKSALLSTNKAVVSLNNGVSVLTISKVLDLKNY-NH2
		136	Ac-NKIKSALLSTNKAVVSLNNGVSVLTISKVLDLKNYI-NH2
		137	Ac-KIKSALLSTNKAVVSLNNGVSVLTISKVLDLKNYID-NH2
5		138	Ac-IKSALLSTNKAVVSLNNGVSVLTISKVLDLKNYIDK-NH2
		139	Ac-KSALLSTNKAVVSLNNGVSVLTISKVLDLKNYIDKQ-NH2
		140	Ac-SALLSTNKAVVSLNNGVSVLTISKVLDLKNYIDKQL-NH2
		141	Ac-ALLSTNKAVVSLNNGVSVLTISKVLDLKNYIDKQLL-NH2
		142	Ac-YTSVITIELSNIKENKCNNGTDAKVLIKQELDKYK-NH2
		143	Ac-TSVITIELSNIKENKCNNGTDAKVLIKQELDKYKN-NH2
		144	Ac-SVITIELSNIKENKCNNGTDAKVLIKQELDKYKNA-NH2
10		145	Ac-VITIELSNIKENKCNNGTDAKVLIKQELDKYKNAV-NH2
		146	Ac-ITIELSNIKENKCNNGTDAKVLIKQELDKYKNAV-NH2
		147	Ac-TIELSNIKENKCNNGTDAKVLIKQELDKYKNAVTE-NH2
		148	Ac-IELSNIKENKCNNGTDAKVLIKQELDKYKNAVTEL-NH2
		149	Ac-ELSNIKENKCNNGTDAKVLIKQELDKYKNAVTELQ-NH2
		150	Ac-LSNIKENKCNNGTDAKVLIKQELDKYKNAVTELQL-NH2
		151	Ac-SNIKENKCNNGTDAKVLIKQELDKYKNAVTELQLL-NH2
15		152	Ac-NIKENKCNNGTDAKVLIKQELDKYKNAVTELQLLM-NH2
		153	Ac-IKENKCNNGTDAKVLIKQELDKYKNAVTELQLLMQ-NH2
		154	Ac-KENKCNNGTDAKVLIKQELDKYKNAVTELQLLMQS-NH2
		155	Ac-ENKCNNGTDAKVLIKQELDKYKNAVTELQLLMQST-NH2
		156	Ac-LLDNFESTWEQSKELWELQEISIQNLHKSALQEYWN-NH2
		157	Ac-ALGVATSAQITA AVALVEAKQARSDIEKLKEAIRD-NH2
		158	Ac-LGVATSAQITA AVALVEAKQARSDIEKLKEAIRDT-NH2
20		159	Ac-GVATSAQITA AVALVEAKQARSDIEKLKEAIRDTN-NH2
		160	Ac-VATSAQITA AVALVEAKQARSDIEKLKEAIRDTNK-NH2
		161	Ac-ATSAQITA AVALVEAKQARSDIEKLKEAIRDTNKA-NH2
		162	Ac-TSAQITA AVALVEAKQARSDIEKLKEAIRDTNKAV-NH2
		163	Ac-SAQITA AVALVEAKQARSDIEKLKEAIRDTNKAVQ-NH2
		164	Ac-AQITA AVALVEAKQARSDIEKLKEAIRDTNKAVQS-NH2
		165	Ac-QITA AVALVEAKQARSDIEKLKEAIRDTNKAVQSV-NH2
25		166	Ac-ITA AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQ-NH2
		167	Ac-TAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQS-NH2
		168	Ac-AAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSS-NH2
		169	Ac-AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSI-NH2
		170	Ac-VALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIG-NH2
		171	Ac-ALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGN-NH2
		172	Ac-LVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNL-NH2
30		173	Ac-VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI-NH2
		174	Ac-EAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIV-NH2
		175	Ac-KQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAI-NH2
		176	Ac-QARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIK-NH2

T No.	Sequence
177	Ac-ARSDIEKLKEAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
178	Ac-RSDIEKLKEAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
179	Ac-SDIEKLKEAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
180	Ac-DIEKLKEAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
5 181	Ac-IEKLKEAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
182	Ac-EKLKEAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
183	Ac-KLKEAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
184	Ac-LKEAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
185	Ac-KEAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
186	Ac-EAIRD TNKAVQSVQSSIGNLIVA IKS-NH2
187	Ac-AIRD TNKAVQSVQSSIGNLIVA IKS-NH2
10 188	Ac-IRD TNKAVQSVQSSIGNLIVA IKS-NH2
189	Ac-YTPNDITLNN SVALDPIDISIELNKA KSDLEESKE-NH2
190	Ac-TPNDITLNN SVALDPIDISIELNKA KSDLEESKEW-NH2
191	Ac-PNDITLNN SVALDPIDISIELNKA KSDLEESKEWI-NH2
192	Ac-NDITLNN SVALDPIDISIELNKA KSDLEESKEWIR-NH2
193	Ac-DITLNN SVALDPIDISIELNKA KSDLEESKEWIRR-NH2
194	Ac-ITLNN SVALDPIDISIELNKA KSDLEESKEWIRRS-NH2
15 195	Ac-TLNN SVALDPIDISIELNKA KSDLEESKEWIRRSN-NH2
196	Ac-LNN SVALDPIDISIELNKA KSDLEESKEWIRRSNQ-NH2
197	Ac-NNN SVALDPIDISIELNKA KSDLEESKEWIRRSNQK-NH2
198	Ac-NSVALDPIDISIELNKA KSDLEESKEWIRRSNQKL-NH2
200	Ac-SVALDPIDISIELNKA KSDLEESKEWIRRSNQKLD-NH2
201	Ac-VALDPIDISIELNKA KSDLEESKEWIRRSNQKLD-NH2
202	Ac-ALDPIDISIELNKA KSDLEESKEWIRRSNQKLD-NH2
20 203	Ac-LDPIDISIELNKA KSDLEESKEWIRRSNQKLD-NH2
204	Ac-DPIDISIELNKA KSDLEESKEWIRRSNQKLD-NH2
205	Ac-PIDISIELNKA KSDLEESKEWIRRSNQKLD-NH2
206	Ac-IDISIELNKA KSDLEESKEWIRRSNQKLD-NH2
207	Ac-DISIELNKA KSDLEESKEWIRRSNQKLD-NH2
208	Ac-ISIELNKA KSDLEESKEWIRRSNQKLD-NH2
209	Ac-SIELNKA KSDLEESKEWIRRSNQKLD-NH2
25 210	Ac-IELNKA KSDLEESKEWIRRSNQKLD-NH2
211	Ac-ELNKA KSDLEESKEWIRRSNQKLD-NH2
212	Ac-ELRALRGELRALRGELRALRGELRALRGELRALRGK-NH2
213	Ac-YTSLIHSLIEESQNQQQKNEQELLELDKWASLWNWF-NH2
214	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
215	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
216	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
30 217	Ac-YTSLIHSLIEESQNQQQKNEQELLELDKWASLWNWF-NH2
218	Ac-EQELLELDKWASLWNWF-NH2
219	Ac-QELLELDKWASLWNWF-NH2
220	Ac-ELLELDKWASLWNWF-NH2

T	No.	Sequence
	221	Ac-LELDKWASLWNWF-NH2
	222	Ac-ELDKWASLWNWF-NH2
	226	Ac-WASLWNWF-NH2
	227	Ac-ASLWNWF-NH2
5	229	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLANAA-NH2
	230	Ac-YTSLIHSLIEESQNQQEKNEQQELLELDKWASLWNWF-NH2
	231	Ac-YTSLIQSLIEESQNQQEKNQQELLELDKWASLWNWF-NH2
	234	Ac-EAAAREAAAREAAARLELDKWASLWNWF-NH2
	236	Ac-PSLRDPISAEISIQALSALGGDINKVLEKLGYSG-NH2
	237	Ac-SLRDPISAEISIQALSALGGDINKVLEKLGYSGG-NH2
	238	Ac-LRDPISAEISIQALSALGGDINKVLEKLGYSGGD-NH2
10	239	Ac-RDPISAEISIQALSALGGDINKVLEKLGYSGGDL-NH2
	240	Ac-DPISAEISIQALSALGGDINKVLEKLGYSGGDLL-NH2
	241	Ac-PISAEISIQALSALGGDINKVLEKLGYSGGDLLG-NH2
	242	Ac-ISAEISIQALSALGGDINKVLEKLGYSGGDLLGI-NH2
	243	Ac-SAEISIQALSALGGDINKVLEKLGYSGGDLLGIL-NH2
	244	Ac-AEISIQALSALGGDINKVLEKLGYSGGDLLGILE-NH2
	245	Ac-EISIQALSALGGDINKVLEKLGYSGGDLLGILES-NH2
15	246	Ac-ISIQALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	247	Ac-SIQALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	248	Ac-IQALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	249	Ac-QALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	250	Ac-ALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	251	Ac-LSALGGDINKVLEKLGYSGGDLLGILES-NH2
	252	Ac-PDAVYLHRIDLGPPISLERLDVGTNLGNIAKLED-NH2
20	253	Ac-DAVYLHRIDLGPPISLERLDVGTNLGNIAKLEDA-NH2
	254	Ac-AVYLHRIDLGPPISLERLDVGTNLGNIAKLEDAK-NH2
	255	Ac-VYLHRIDLGPPISLERLDVGTNLGNIAKLEDAKE-NH2
	256	Ac-YLHRIDLGPPISLERLDVGTNLGNIAKLEDAKEL-NH2
	257	Ac-LHRIDLGPPISLERLDVGTNLGNIAKLEDAKELL-NH2
	258	Ac-HRIDLGPPISLERLDVGTNLGNIAKLEDAKELLE-NH2
	259	Ac-RIDLGPPISLERLDVGTNLGNIAKLEDAKELLES-NH2
25	260	Ac-IDLGPPISLERLDVGTNLGNIAKLEDAKELLESS-NH2
	261	Ac-DLGPPISLERLDVGTNLGNIAKLEDAKELLESSD-NH2
	262	Ac-LGPPISLERLDVGTNLGNIAKLEDAKELLESSDQ-NH2
	263	Ac-GPPISLERLDVGTNLGNIAKLEDAKELLESSDQI-NH2
	264	Ac-PPISLERLDVGTNLGNIAKLEDAKELLESSDQIL-NH2
	265	Ac-PISLERLDVGTNLGNIAKLEDAKELLESSDQILR-NH2
	266	Ac-ISLERLDVGTNLGNIAKLEDAKELLESSDQIRS-NH2
30	267	Ac-SLERLDVGTNLGNIAKLEDAKELLESSDQILRSM-NH2
	268	Ac-LERLDVGTNLGNIAKLEDAKELLESSDQILRSMK-NH2
	269	Ac-EWIRRSNQKLDSE-NH2
	270	Ac-LELDKWASLANAF-NH2

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No.	Sequence
271	Ac-LELDKWASLFNFF-NH2
272	Ac-LELDKWASLANWF-NH2
273	Ac-LELDKWASLWNAF-NH2
274	Ac-ELGNVNNSISNALDKLEESNSKLDKVN VKLTSTSA-NH2
5 275	Ac-TELGNVNNSISNALDKLEESNSKLDKVN VKLTSTS-NH2
276	Ac-STELGNVNNSISNALDKLEESNSKLDKVN VKLTST-NH2
277	Ac-ISTELGNVNNSISNALDKLEESNSKLDKVN VKLTS-NH2
278	Ac-DISTELGNVNNSISNALDKLEESNSKLDKVN VKLT-NH2
279	Ac-LDISTELGNVNNSISNALDKLEESNSKLDKVN VKL-NH2
280	Ac-NLDISTELGNVNNSISNALDKLEESNSKLDKVN VK-NH2
281	Ac-GNLDISTELGNVNNSISNALDKLEESNSKLDKVN V-NH2
10 282	Ac-TGNLDISTELGNVNNSISNALDKLEESNSKLDKVN-NH2
283	Ac-VTGNLDISTELGNVNNSISNALDKLEESNSKLDKV-NH2
284	Ac-IVTGNLDISTELGNVNNSISNALDKLEESNSKLDK-NH2
285	Ac-VIVTGNLDISTELGNVNNSISNALDKLEESNSKLD-NH2
286	Ac-QVIVTGNLDISTELGNVNNSISNALDKLEESNSKL-NH2
287	Ac-SQVIVTGNLDISTELGNVNNSISNALDKLEESNSK-NH2
288	Ac-DSQVIVTGNLDISTELGNVNNSISNALDKLEESNS-NH2
15 289	Ac-LDSQVIVTGNLDISTELGNVNNSISNALDKLEESN-NH2
290	Ac-ILDSQVIVTGNLDISTELGNVNNSISNALDKLEES-NH2
291	Ac-SILDSQVIVTGNLDISTELGNVNNSISNALDKLEE-NH2
292	Ac-ISILDSQVIVTGNLDISTELGNVNNSISNALDKLE-NH2
293	Ac-NISILDSQVIVTGNLDISTELGNVNNSISNALDKL-NH2
294	Ac-KNISILDSQVIVTGNLDISTELGNVNNSISNALDK-NH2
295	Ac-QKNISILDSQVIVTGNLDISTELGNVNNSISNALD-NH2
20 296	Ac-YQKNISILDSQVIVTGNLDISTELGNVNNSISNAL-NH2
297	Ac-TYQKNISILDSQVIVTGNLDISTELGNVNNSISNA-NH2
298	Ac-ATYQKNISILDSQVIVTGNLDISTELGNVNNSISN-NH2
299	Ac-DATYQKNISILDSQVIVTGNLDISTELGNVNNSIS-NH2
300	Ac-FDATYQKNISILDSQVIVTGNLDISTELGNVNNSI-NH2
301	Ac-EFDATYQKNISILDSQVIVTGNLDISTELGNVNNS-NH2
302	Ac-GEFDATYQKNISILDSQVIVTGNLDISTELGNVNN-NH2
25 303	Ac-SGEFDATYQKNISILDSQVIVTGNLDISTELGNVN-NH2
304	Ac-LSGEFDATYQKNISILDSQVIVTGNLDISTELGNV-NH2
305	Ac-RLSGEFDATYQKNISILDSQVIVTGNLDISTELGN-NH2
306	Ac-LRLSGEFDATYQKNISILDSQVIVTGNLDISTELG-NH2
307	Ac-TLRLSGEFDATYQKNISILDSQVIVTGNLDISTEL-NH2
308	Ac-ITLRLSGEFDATYQKNISILDSQVIVTGNLDISTE-NH2
309	Ac-GITLRLSGEFDATYQKNISILDSQVIVTGNLDIST-NH2
30 310	Ac-TATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFNNT-NH2
311	Ac-ITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFNN-NH2
312	Ac-SITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFN-NH2
314	Ac-KESITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQ-NH2

T	
No.	Sequence
315	Ac-LKESITATIEAVHEVTDGLSQLAVAVGKMQQFVND-NH2
316	Ac-RLKESITATIEAVHEVTDGLSQLAVAVGKMQQFVN-NH2
317	Ac-LRLKESITATIEAVHEVTDGLSQLAVAVGKMQQFV-NH2
318	Ac-ILRLKESITATIEAVHEVTDGLSQLAVAVGKMQQF-NH2
5 319	Ac-NILRLKESITATIEAVHEVTDGLSQLAVAVGKMQQ-NH2
320	Ac-ANILRLKESITATIEAVHEVTDGLSQLAVAVGKM-Q-NH2
321	Ac-AANILRLKESITATIEAVHEVTDGLSQLAVAVGKM-NH2
322	Ac-HKCDDECMNSVKNGTYDYPKYEEESKLNREIKGV-NH2
323	Ac-KCDECMNSVKNGTYDYPKYEEESKLNREIKGVK-NH2
324	Ac-CDDECMNSVKNGTYDYPKYEEESKLNREIKGVKL-NH2
325	Ac-DDECMNSVKNGTYDYPKYEEESKLNREIKGVKLS-NH2
10 326	Ac-DECMNSVKNGTYDYPKYEEESKLNREIKGVKLSS-NH2
327	Ac-ECMNSVKNGTYDYPKYEEESKLNREIKGVKLSSM-NH2
328	Ac-CMNSVKNGTYDYPKYEEESKLNREIKGVKLSSMG-NH2
329	Ac-MNSVKNGTYDYPKYEEESKLNREIKGVKLSSMGV-NH2
330	Ac-NSVKNGTYDYPKYEEESKLNREIKGVKLSSMGVY-NH2
331	Ac-SVKNGTYDYPKYEEESKLNREIKGVKLSSMGVYQ-NH2
332	Ac-VKNGTYDYPKYEEESKLNREIKGVKLSSMGVYQI-NH2
15 333	Ac-KNGTYDYPKYEEESKLNREIKGVKLSSMGVYQIL-NH2
334	Ac-AFIRKSDELLHNV-NH2
335	Ac-VVLGAALGVATAAQITAGIALHQSMNLNSQAIDNL-NH2
336	Ac-VLAGAALGVATAAQITAGIALHQSMNLNSQAIDNLR-NH2
337	Ac-LAGAALGVATAAQITAGIALHQSMNLNSQAIDNLRA-NH2
338	Ac-AGAALGVATAAQITAGIALHQSMNLNSQAIDNLRAS-NH2
339	Ac-GAALGVATAAQITAGIALHQSMNLNSQAIDNLRASL-NH2
20 340	Ac-AALGVATAAQITAGIALHQSMNLNSQAIDNLRASLE-NH2
341	Ac-ALGVATAAQITAGIALHQSMNLNSQAIDNLRASLET-NH2
342	Ac-LGVATAAQITAGIALHQSMNLNSQAIDNLRASLETT-NH2
343	Ac-GVATAAQITAGIALHQSMNLNSQAIDNLRASLETTN-NH2
344	Ac-VATAAQITAGIALHQSMNLNSQAIDNLRASLETTNQ-NH2
345	Ac-ATAAQITAGIALHQSMNLNSQAIDNLRASLETTNQAI-NH2
25 346	Ac-TAAQITAGIALHQSMNLNSQAIDNLRASLETTNQAI-NH2
347	Ac-AAQITAGIALHQSMNLNSQAIDNLRASLETTNQAIENH2
348	Ac-AQITAGIALHQSMNLNSQAIDNLRASLETTNQAIENH2
349	Ac-QITAGIALHQSMNLNSQAIDNLRASLETTNQAIENH2
350	Ac-ITAGIALHQSMNLNSQAIDNLRASLETTNQAIENH2
351	Ac-TAGIALHQSMNLNSQAIDNLRASLETTNQAIENH2
352	Ac-AGIALHQSMNLNSQAIDNLRASLETTNQAIENH2
353	Ac-GIALHQSMNLNSQAIDNLRASLETTNQAIENH2
30 354	Ac-IALHQSMNLNSQAIDNLRASLETTNQAIENH2
355	Ac-ALHQSMNLNSQAIDNLRASLETTNQAIENH2
356	Ac-LHQSMNLNSQAIDNLRASLETTNQAIENH2
357	Ac-HQSMNLNSQAIDNLRASLETTNQAIENH2

T	No.	Sequence
	358	Ac-QSMLNSQAIDNLRASLETTNQAIEAIRQAGQEMIL-NH2
	359	Ac-SMLNSQAIDNLRASLETTNQAIEAIRQAGQEMILA-NH2
	360	Ac-MLNSQAIDNLRASLETTNQAIEAIRQAGQEMILAV-NH2
	361	Ac-LNSQAIDNLRASLETTNQAIEAIRQAGQEMILAVQ-NH2
5	362	Ac-NSQAIDNLRASLETTNQAIEAIRQAGQEMILAVQG-NH2
	363	Ac-SQAIDNLRASLETTNQAIEAIRQAGQEMILAVQGV-NH2
	364	Ac-QAIDNLRASLETTNQAIEAIRQAGQEMILAVQGVQ-NH2
	365	Ac-AIDNLRASLETTNQAIEAIRQAGQEMILAVQGVQD-NH2
	366	Ac-IDNLRASLETTNQAIEAIRQAGQEMILAVQGVQDY-NH2
	367	Ac-DNLRASLETTNQAIEAIRQAGQEMILAVQGVQDYI-NH2
	368	Ac-NLRASLETTNQAIEAIRQAGQEMILAVQGVQDYIN-NH2
10	369	Ac-LRASLETTNQAIEAIRQAGQEMILAVQGVQDYINN-NH2
	370	Ac-RASLETTNQAIEAIRQAGQEMILAVQGVQDYINNE-NH2
	371	Ac-YTSVITIELSNIKENKUNGTDVAVKLIKQELDKYK-NH2
	372	Ac-TSVITIELSNIKENKUNGTDVAVKLIKQELDKYKN-NH2
	373	Ac-SVITIELSNIKENKUNGTDVAVKLIKQELDKYKNA-NH2
	374	Ac-SNIKENKUNGTDVAVKLIKQELDKYKNAVTELQLL-NH2
	375	Ac-KENKUNGTDVAVKLIKQELDKYKNAVTELQLLMQS-NH2
15	376	Ac-CLELDKWASLWNWFC-NH2
	377	Ac-CLELDKWASLANWFC-NH2
	378	Ac-CLELDKWASLFNFFC-NH2
	379	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLFNFF-NH2
	381	Ac-RMKQLEDKVEELLSKNYHLENELELDKWASLWNWF-NH2
	382	Ac-KVEELLSKNYHLENELELDKWASLWNWF-NH2
	383	Ac-RMKQLEDKVEELLSKLEWIRRSNQKLDISI-NH2
20	384	Ac-RMKQLEDKVEELLSKLAFIRKSDELHNV-NH2
	385	Ac-ELEALRGELRALRGELDELDKWASLWNWF-NH2
	386	Ac-LDPIDISIELNKAUSDLEESKEWIRRSNQKLDISI-NH2
	387	Ac-CNEQLSDSFPVEFFQV-NH2
	388	Ac-MAEDDPYLGRPEQMFHLDPSL-NH2
	389	Ac-EDFSSIADMDFSALLSQISS-NH2
	390	Ac-TWQEWERKVD FLEENITALLLEEAQIQQEKMYELQ-NH2
25	391	Ac-WQEWERKVD FLEENITALLLEEAQIQQEKMYELQK-NH2
	392	Ac-QEWERKVD FLEENITALLLEEAQIQQEKMYELQKL-NH2
	393	Ac-EWERKVD FLEENITALLLEEAQIQQEKMYELQKLN-NH2
	394	Ac-WERKVD FLEENITALLLEEAQIQQEKMYELQKLNS-NH2
	395	Ac-ERKVD FLEENITALLLEEAQIQQEKMYELQKLNSW-NH2
	396	Ac-RKVD FLEENITALLLEEAQIQQEKMYELQKLNSWD-NH2
	397	Ac-KVD FLEENITALLLEEAQIQQEKMYELQKLNSWDV-NH2
30	398	Ac-VDFLEENITALLLEEAQIQQEKMYELQKLNSWDVF-NH2
	399	Ac-DFLEENITALLLEEAQIQQEKMYELQKLNSWDVFG-NH2
	400	Ac-FLEENITALLLEEAQIQQEKMYELQKLNSWDVFGN-NH2
	401	Ac-LEENITALLLEEAQIQQEKMYELQKLNSWDVFGNW-NH2

T		No.	Sequence
		402	Ac-LEENITALLEEAIQQEKNMYELQKLSWDVFGNWF-NH2
		403	Ac-NEQSEEKENELYWAKEQLLDLLFNIFNQTVGAWIMQ-NH2
		405	Ac-QQQLLDVVKRQQEELLRLTVWGTKNLQTRVTAIEKYLKD-NH2
		406	Ac-QQQLLDVVKRQQEELLRLTVWGTKNLQTRVTAIEKYLKDQ-NH2
5		407	Ac-QQQLLDVVKRQQEELLRLTVWGPKNLQTRVTAIEKYLKDQ-NH2
		408	Ac-DERKQDKVLVVQQTGTLQLTLIQLEKTAKLQWVRLNRY-NH2
		409	Ac-QQQLLDVVKRQQEELLRLTVWGTKNLQTRVTAIEKY-NH2
		410	Ac-QQQLLDVVKRQQEELLRLTVWGTKNLQTRVTAIEKYL-NH2
		411	Ac-QLLDVVKRQQEELLRLTVWGTKNLQTRVTAIEKYLK-NH2
		412	Ac-LLDVVKRQQEELLRLTVWGTKNLQTRVTAIEKYLKD-NH2
		413	Ac-LDVVKRQQEELLRLTVWGTKNLQTRVTAIEKYLKDQ-NH2
10		414	Ac-DVVVKRQQEELLRLTVWGTKNLQTRVTAIEKYLKDQA-NH2
		415	Ac-VVKRQQEELLRLTVWGTKNLQTRVTAIEKYLKDQAQ-NH2
		416	Ac-VKRQQEELLRLTVWGTKNLQTRVTAIEKYLKDQAQL-NH2
		417	Ac-KRQQEELLRLTVWGTKNLQTRVTAIEKYLKDQAQLN-NH2
		418	Ac-RQQEELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNA-NH2
		419	Ac-QQEELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNAW-NH2
		420	Ac-QEELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNAWG-NH2
15		421	Ac-ELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNAWGC-NH2
		422	Ac-NNLLRAIEAQHLLQLTVWGPKQLQARILAVERYLKDQ-NH2
		423	Ac-SELEIKRYKNRVASRKCRKFKQLLQHYREVAAAK-NH2
		424	Ac-ELEIKRYKNRVASRKCRKFKQLLQHYREVAAAKS-NH2
		425	Ac-LEIKRYKNRVASRKCRKFKQLLQHYREVAAAKSS-NH2
		426	Ac-EIKRYKNRVASRKCRKFKQLLQHYREVAAAKSSE-NH2
		427	Ac-IKRYKNRVASRKCRKFKQLLQHYREVAAAKSSEN-NH2
20		428	Ac-KRYKNRVASRKCRKFKQLLQHYREVAAAKSSEND-NH2
		429	Ac-RYKNRVASRKCRKFKQLLQHYREVAAAKSENDR-NH2
		430	Ac-YKNRVASRKCRKFKQLLQHYREVAAAKSENDR-L-NH2
		431	Ac-KNRVASRKCRKFKQLLQHYREVAAAKSENDR-LR-NH2
		432	Ac-NRVASRKCRKFKQLLQHYREVAAAKSENDR-LRL-NH2
		433	Ac-RVASRKCRKFKQLLQHYREVAAAKSENDR-LRLL-NH2
		434	Ac-VASRKCRKFKQLLQHYREVAAAKSENDR-LRLLL-NH2
25		435	Ac-ASRKCRKFKQLLQHYREVAAAKSENDR-LRLLLK-NH2
		436	Ac-SRKCRKFKQLLQHYREVAAAKSENDR-LRLLLKQ-NH2
		437	Ac-RKCRKFKQLLQHYREVAAAKSENDR-LRLLLKQM-NH2
		438	Ac-KCRKFKQLLQHYREVAAAKSENDR-LRLLLKQMC-NH2
		439	Ac-CRKFKQLLQHYREVAAAKSENDR-LRLLLKQMCP-NH2
		440	Ac-RAKFKQLLQHYREVAAAKSENDR-LRLLLKQMCP-S-NH2
		441	Ac-AKFKQLLQHYREVAAAKSENDR-LRLLLKQMCP-SL-NH2
30		442	Ac-KFKQLLQHYREVAAAKSENDR-LRLLLKQMCP-SLD-NH2
		443	Ac-FKQLLQHYREVAAAKSENDR-LRLLLKQMCP-SLDV-NH2
		444	Ac-KQLLQHYREVAAAKSENDR-LRLLLKQMCP-SLDVD-NH2
		445	Ac-QLLQHYREVAAAKSENDR-LRLLLKQMCP-SLDVDS-NH2

T No.	Sequence
446	Ac-LLQHYREVAAAKSSSENDRLRLLKQMCPSLDVDSI-NH2
447	Ac-LQHYREVAAAKSSSENDRLRLLKQMCPSLDVDSII-NH2
448	Ac-QHYREVAAAKSSSENDRLRLLKQMCPSLDVDSIIP-NH2
449	Ac-HYREVAAAKSSSENDRLRLLKQMCPSLDVDSIIPR-NH2
5 450	Ac-YREVAAAKSSSENDRLRLLKQMCPSLDVDSIIPRT-NH2
451	Ac-REVAAAKSSSENDRLRLLKQMCPSLDVDSIIPRTP-NH2
452	Ac-EVAAAKSSSENDRLRLLKQMCPSLDVDSIIPRTPD-NH2
453	Ac-VAAAKSSSENDRLRLLKQMCPSLDVDSIIPRTPDV-NH2
454	Ac-AAAKSSSENDRLRLLKQMCPSLDVDSIIPRTPDVL-NH2
455	Ac-AAKSSSENDRLRLLKQMCPSLDVDSIIPRTPDVLH-NH2
456	Ac-AKSSSENDRLRLLKQMCPSLDVDSIIPRTPDVLHE-NH2
10 457	Ac-KSSSENDRLRLLKQMCPSLDVDSIIPRTPDVLHED-NH2
458	Ac-SSSENDRLRLLKQMCPSLDVDSIIPRTPDVLHEDL-NH2
459	Ac-SENDRLRLLKQMCPSLDVDSIIPRTPDVLHEDLL-NH2
460	Ac-ENDRLRLLKQMCPSLDVDSIIPRTPDVLHEDLLN-NH2
461	Ac-NDRLRLLKQMCPSLDVDSIIPRTPDVLHEDLLNF-NH2
534	Ac-PGYRWMCLRRFIIIFLFIILLCLIFLLVLLDYQGML-NH2
535	Ac-GYRWMCLRRFIIIFLFIILLCLIFLLVLLDYQGMLP-NH2
15 536	Ac-YRWMCLRRFIIIFLFIILLCLIFLLVLLDYQGMLPV-NH2
537	Ac-RWMCLRRFIIIFLFIILLCLIFLLVLLDYQGMLPVC-NH2
538	Ac-WMCLRRFIIIFLFIILLCLIFLLVLLDYQGMLPVCP-NH2
539	Ac-MCLRRFIIIFLFIILLCLIFLLVLLDYQGMLPVCPCL-NH2
540	Ac-CLRRFIIIFLFIILLCLIFLLVLLDYQGMLPVCPCLI-NH2
541	Ac-LRRFIIIFLFIILLCLIFLLVLLDYQGMLPVCPCLIP-NH2
542	Ac-RRFIIIFLFIILLCLIFLLVLLDYQGMLPVCPCLIPG-NH2
20 543	Ac-RFIIIFLFIILLCLIFLLVLLDYQGMLPVCPCLIPGS-NH2
544	Ac-FIIIFLFIILLCLIFLLVLLDYQGMLPVCPCLIPGSS-NH2
545	Ac-IIIFLFIILLCLIFLLVLLDYQGMLPVCPCLIPGSST-NH2
546	Ac-IFLFIILLCLIFLLVLLDYQGMLPVCPCLIPGSSTT-NH2
547	Ac-FLFIILLCLIFLLVLLDYQGMLPVCPCLIPGSSTTS-NH2
548	Ac-LFIILLCLIFLLVLLDYQGMLPVCPCLIPGSSTTST-NH2
549	Ac-FIILLCLIFLLVLLDYQGMLPVCPCLIPGSSTTSTG-NH2
25 550	Ac-ILLCLIFLLVLLDYQGMLPVCPCLIPGSSTTSTGP-NH2
551	Ac-LLLCLIFLLVLLDYQGMLPVCPCLIPGSSTTSTGPC-NH2
552	Ac-LLCLIFLLVLLDYQGMLPVCPCLIPGSSTTSTGPCR-NH2
553	Ac-LCLIFLLVLLDYQGMLPVCPCLIPGSSTTSTGPCRT-NH2
554	Ac-CLIFLLVLLDYQGMLPVCPCLIPGSSTTSTGPCRTC-NH2
555	Ac-LIFLLVLLDYQGMLPVCPCLIPGSSTTSTGPCRTCMT-NH2
556	Ac-IFLLVLLDYQGMLPVCPCLIPGSSTTSTGPCRTCMT-NH2
30 557	Ac-FLLVLLDYQGMLPVCPCLIPGSSTTSTGPCRTCMTT-NH2
558	Ac-PPLVLQAGFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
559	Ac-LLVLQAGFLLTRILTIPQSLDSWWTSLNFLGGTT-NH2
560	Ac-LVLQAGFLLTRILTIPQSLDSWWTSLNFLGGTTV-NH2

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No.	Sequence
561	Ac-VLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVC-NH2
562	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCL-NH2
563	Ac-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-NH2
564	Ac-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-NH2
5 565	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-NH2
566	Ac-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-NH2
567	Ac-PLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-NH2
568	Ac-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-NH2
569	Ac-LTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQSP-NH2
570	Ac-FWNWLSAWKDLELKSLEEVKDELQKMR-NH2
571	Ac-NNLLRAIEAQQHLLQLTVW-NH2
10 572	Ac-CGGNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
573	Ac-YTSLIHSLEESQNQQEKNEQELLELDKASLWNNWF-NH2
574	C13H27CO-YTSLIHSLEESQNQQEKNEQELLELDKASLWNNWF-NH2
575	Ac-AVSKGYLSALRTGWYTSVITIELSNIKENKUNGTD-NH2
576	Ac-SISNIETVIEFQQKNNRLEITREFSVNAGVTTTPVS-NH2
577	Ac-DQQIKQYKRLLDRLIIPLYDGLRQKDVIVSNQESN-NH2
578	Ac-YSELTNIFGDNIGSLQEKGIKLGQIASLYRTNITEI-NH2
15 579	Ac-TSITLQVRLPLLTRLNLTQIYRVDSISYNIQNREWY-NH2
580	Ac-VEIAEYRLLRLTVLEPIRDALNAMTQNIQNPVQSV-NH2
581	Ac-SYFIVLSIAYPTLSEIKGVIVHRLEGVSYNIGSQEW-NH2
582	Ac-LKEAIRDTNKAVQSVQSSIGNLIVAIS-NH2
583	NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
583	NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
584	QKQEPIDKELYPLTSL
20 585	YPKFVKQNTLKLAT
586	QYIKANQKFIGITE
587	NGQIGNDPNRDILY
588	AC-RPDVY-OH
589	CLELDKASLWNNWFC- (cyclic)
590	CLELDKASLANWFC- (cyclic)
591	CLELDKASLANFFC- (cyclic)
25 594	Ac-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
595	Ac-CGGYTSLEIHSLEESQNQQEKNEQELLELDKASLWNNWF-NH2
596	Ac-PLLVQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
597	Ac-LLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTT-NH2
598	Ac-LVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTV-NH2
599	Ac-VLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVC-NH2
600	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCL-NH2
30 601	Ac-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-NH2
602	Ac-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-NH2
603	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-NH2
604	Ac-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-NH2

T	No.	Sequence
	605	Ac-FLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-NH2
	606	Ac-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-NH2
	607	Ac-LTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQSP-NH2
	608	Ac-LELDKWASLWNWA-NH2
5	609	Ac-LELDKWAASLWNWF-NH2
	610	Ac-LELDKAASLWNWF-NH2
	611	Ac-LKLDKWASLWNWF-NH2
	612	Ac-LELKKWASLWNWF-NH2
	613	Ac-DELLHNVNAGKST-NH2
	614	Ac-KSDELLHNVNAGKST-NH2
	615	Ac-IRKSDELLHNVNAGKST-NH2
10	616	Ac-AFIRKSDELLHNVNAGKST-NH2
	617	Ac-FDASISQVNEKINQSLAFI-NH2
	618	Ac-YAADKESTQKAFDGITNKVNSVIEKMNTQFEAVGKE-NH2
	619	Ac-SVIEKMNTQFEAVGKEFGNLERLENLNKRMEDGFL-NH2
	620	Ac-VWTYNAELLVLMENERTLDFHDSNVKNLYDKVRMQL-NH2
	621	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEGGC-NH2
	622	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
15	623	Ac-INNYTSLIHSLIEESQNQQEKNEQELLE-NH2
	624	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
	625	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	626	Ac-IDISIELNKAASDLEESKEWIKKSNQKLD SIGNWH-NH2
	627	Ac-NQQEKNEQELLELDKWASLWNWFNITNWLWYIKIFI-NH2
	627	Ac-NQQEKNEQELLELDKWASLWNWFNITNWLWYIKIFI-NH2
	628	Ac-QNQQEKNEQELLELDKWASLWNWFNITNWLWYIKIF-NH2
20	629	Ac-SQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKI-NH2
	630	Ac-ESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIK-NH2
	631	Ac-EESQNQQEKNEQELLELDKWASLWNWFNITNWLWYI-NH2
	632	Ac-IEESQNQQEKNEQELLELDKWASLWNWFNITNWLWY-NH2
	633	Ac-LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLW-NH2
	634	Ac-SLIEESQNQQEKNEQELLELDKWASLWNWFNITNWL-NH2
	635	Ac-HSLIEESQNQQEKNEQELLELDKWASLWNWFNITNW-NH2
25	636	Ac-IHSLIEESQNQQEKNEQELLELDKWASLWNWFNITN-NH2
	637	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNWFNIT-NH2
	638	Ac-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-NH2
	639	Ac-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2
	640	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-NH2
	641	Ac-NNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-NH2
	642	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW-NH2
30	643	Ac-EINNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
	644	Ac-REINNYTSLIHSLIEESQNQQEKNEQELLELDKWAS-NH2
	645	Ac-DREINNYTSLIHSLIEESQNQQEKNEQELLELDKWA-NH2
	646	Ac-WDREINNYTSLIHSLIEESQNQQEKNEQELLELDKW-NH2

T	No.	Sequence
	647	Ac-EWDREINNYTSLIHSLEESQNQQEKNEQELLELDK-NH2
	648	Ac-MEWDREINNYTSLIHSLEESQNQQEKNEQELLELD-NH
	649	Ac-WMEWDREINNYTSLIHSLEESQNQQEKNEQELLELD-NH2
	650	Ac-TWMEWDREINNYTSLIHSLEESQNQQEKNEQELLE-NH2
5	651	Ac-MTWMEWDREINNYTSLIHSLEESQNQQEKNEQELL-NH2
	652	Ac-NMTWMEWDREINNYTSLIHSLEESQNQQEKNEQEL-NH2
	653	Ac-NNMTWMEWDREINNYTSLIHSLEESQNQQEKNEQE-NH2
	654	Ac-WNNMTWMEWDREINNYTSLIHSLEESQNQQEKNEQ-NH2
	655	Ac-IWNNMTWMEWDREINNYTSLIHSLEESQNQQEKNE-NH2
	656	Ac-QIWNNMTWMEWDREINNYTSLIHSLEESQNQQEKN-NH2
	657	Ac-EQIWNNMTWMEWDREINNYTSLIHSLEESQNQQEK-NH2
10	658	Ac-LEQIWNNMTWMEWDREINNYTSLIHSLEESQNQQE-NH2
	659	Ac-SLEQIWNNMTWMEWDREINNYTSLIHSLEESQNQQ-NH2
	660	Ac-KSLEQIWNNMTWMEWDREINNYTSLIHSLEESQNQ-NH2
	661	Ac-NKSLEQIWNNMTWMEWDREINNYTSLIHSLEESQN-NH2
	662	Ac-SLAFIRKSDHELLHNVNAGKST-NH2
	663	Ac-FDASISQVNEKINQSLAFIRK-NH2
	664	Ac-YTSLIHSLEESQQQEKQEQELLELDKQASLWNWF-NH2
15	665	Ac-FDASISQVNEKINQSLAFIRKSDHELLHNVNAGK-NH2
	666	Ac-FDASISQVNEKINQSLAFIRKSDHELLHNVNA-NH2
	667	Ac-FDASISQVNEKINQSLAFIRKSDHELLHNV-NH2
	668	Ac-FDASISQVNEKINQSLAFIRKSDHELLH-NH2
	669	Ac-FDASISQVNEKINQSLAFIRKSDDEL-NH2
	670	Ac-FDASISQVNEKINQSLAFIRKSD-NH2
	671	Ac-ASISQVNEKINQSLAFIRKSDHELLHNVNAGKST-NH2
20	672	Ac-ISQVNEKINQSLAFIRKSDHELLHNVNAGKST-NH2
	673	Ac-QVNEKINQSLAFIRKSDHELLHNVNAGKST-NH2
	674	Ac-NEKINQSLAFIRKSDHELLHNVNAGKST-NH2
	675	Ac-KINQSLAFIRKSDHELLHNVNAGKST-NH2
	676	Ac-NQSLAFIRKSDHELLHNVNAGKST-NH2
	677	Ac-FWNWLSAWKDLELYPGSLELDKQASLWNWF-NH2
	678	Ac-CGGNNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
25	679	Ac-CGGYTSLIHSLEESQNQQEKNEQELLELDKQASLWNWF-NH2
	680	YTSLIHSLEESQNQQEKNEQELLELDKQASLWNWF
	681	NNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ
	682	Ac-EKNMYELQKLNWDVFTNWLDFTSWVRYIQYIQGV-NH2
	683	Ac-QEKNMYELQKLNWDVFTNWLDFTSWVRYIQYIQY-NH2
	684	Ac-QQEKMYELQKLNWDVFTNWLDFTSWVRYIQYIQY-NH2
	685	Ac-IQQEKMYELQKLNWDVFTNWLDFTSWVRYIQYIQ-NH2
30	686	Ac-QIQQEKMYELQKLNWDVFTNWLDFTSWVRYIQYI-NH2
	687	Ac-AQIQQEKMYELQKLNWDVFTNWLDFTSWVRYIQY-NH2
	688	Ac-QAQIQQEKMYELQKLNWDVFTNWLDFTSWVRYIQ-NH2
	689	Ac-EQAQIQQEKMYELQKLNWDVFTNWLDFTSWVRYI-NH2

T	No.	Sequence
	690	Ac-LEQAQIQQEKMYELQKLNWDVFTNWLDFTSWVRY-NH2
	691	Ac-SLEQAQIQQEKMYELQKLNWDVFTNWLDFTSWVR-NH2
	692	Ac-QSLEQAQIQQEKMYELQKLNWDVFTNWLDFTSWV-NH2
	693	Ac-SQSLEQAQIQQEKMYELQKLNWDVFTNWLDFTSW-NH2
5	694	Ac-ISQSLEQAQIQQEKMYELQKLNWDVFTNWLDFTS-NH2
	695	Ac-NISQSLEQAQIQQEKMYELQKLNWDVFTNWLDFT-NH2
	696	Ac-ANISQSLEQAQIQQEKMYELQKLNWDVFTNWLD-NH2
	697	Ac-EANISQSLEQAQIQQEKMYELQKLNWDVFTNWLD-NH2
	699	Ac-YLEANISQSLEQAQIQQEKMYELQKLNWDVFTNW-NH2
	700	Ac-YTSLIHSLIEESQNQQEKNEQEL-NH2
	701	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
10	702	Ac-YTSLIHSLIEESQNQQEKLEQELLELDKWASLWNWF-NH2
	703	Ac-YTSLIHSLIEESQNQQEKNEQELLEFDKWASLWNWF-NH2
	704	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKPASLWNWF-NH2
	705	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	706	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNSF-NH2
	707	Biotin NH(CH2)4CO-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	708	Biotin NH(CH2)6CO-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
15	709	FMOC-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF
	710	FMOC-NNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ
	711	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
	712	Ac-LIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	713	Ac-FWNWLSAWKDLELGGPGSGPGGLELDKWASLWNWF-NH2
	714	Ac-LIHSLIEESQNQQEKNEQELLELDKWASL-NH2
	715	Ac-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
20	716	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	718	FMOC-GGGGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	719	Ac-HSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	720	Ac-YTSLIYSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	721	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	722	Ac-YTSLIHSSIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	723	Ac-LEANISQLLEQAQIQQEKMYELQKLNWDVFTNWL-NH2
25	724	Ac-SLEECDSELEIKRYKNRVASRKCRKFKQLLOHYR-NH2
	725	Ac-LEECDSELEIKRYKNRVASRKCRKFKQLLOHYRE-NH2
	726	Ac-EECDSELEIKRYKNRVASRKCRKFKQLLOHYREV-NH2
	727	Ac-ECDSELEIKRYKNRVASRKCRKFKQLLOHYREVA-NH2
	728	Ac-CDSELEIKRYKNRVASRKCRKFKQLLOHYREVAAA-NH2
	729	Ac-DSELEIKRYKNRVASRKCRKFKQLLOHYREVAAA-NH2
	730	Desaminotyrosine-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
30	731	WASLWNW-NH2
	732	Ac-EAQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIW-NH2
	733	Ac-IEAQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIW-NH2
	734	Ac-AIEAQHLLQLTVWGIKQLQARILAVERYLKDQQLLGI-NH2

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No.	Sequence
735	Ac-RAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLG-NH2
736	Ac-LRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLL-NH2
737	Ac-LLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQL-NH2
738	Ac-NLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQ-NH2
5 739	Ac-QNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKD-NH2
740	Ac-QQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLK-NH2
741	Ac-QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYL-NH2
742	Ac-VQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2
743	Ac-IVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVER-NH2
744	Ac-GIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVE-NH2
745	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAV-NH2
10 758	Ac-RSMTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTV-NH2
760	Ac-GARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQL-NH2
764	Ac-GSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQH-NH2
765	Ac-GSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQH-NH2
766	Ac-EGSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQ-NH2
767	Ac-RAKFKQLLQHYREVAAAKSSSENDRLRL-L-NH2
768	Ac-AKFKQLLQHYREVAAAKSSSENDRLRL-L-NH2
15 769	Ac-KFKQLLQHYREVAAAKSSSENDRLRL-L-L-NH2
770	Ac-PKQLLQHYREVAAAKSSSENDRLRL-L-L-L-NH2
771	Ac-RAKFKQELQHYREVAAAKSSSENDRLRL-L-L-L-QMCP-S-NH2
772	DKWASLWNWF-NH2
773	Biotin-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
774	Ac-YDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
775	Ac-YDASISQVNEKINQSLAYIRKSDELLHNVNAGKST-NH2
20 776	Ac-FDASISQVNEKINQSLAYIRKSDELLHNVNAGKST-NH2
777	Ac-FDASISQVQEKIQQSLAFIRKSDELLHQVQAGKST-NH2
778	Ac-FDASISQVNEKINQALAFIRKADELHNVNAGKST-NH2
779	Ac-FDASISQVNEKINQALAFIRKSDELLHNVNAGKST-NH2
780	Ac-FDASISQVNEKINQSLAFIRKADELHNVNAGKST-NH2
781	Ac-YDASISQVQEEIQQALAFIRKADELLEQVQAGKST-NH2
782	Ac-FDASISQVNEKINQSLAFIRKSDELLENVNAGKST-NH2
25 783	Ac-FDASISQVNEEINQSLAFIRKSDELLHNVNAGKST-NH2
784	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLENV-NH2
785	Ac-VFPSDEFDASISQVNEEINQSLAFIRKSDELLENV-NH2
786	Ac-VFPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
787	Ac-VFPSDEFDASISQVNEEINQSLAFIRKSDELLHNV-NH2
788	Ac-SNKSLEQIWNMTWMEWDREINNYTSLIHSLIEESQ-NH2
789	Ac-WSNKSLEQIWNMTWMEWDREINNYTSLIHSLIEES-NH2
30 790	Ac-SWSNKSLEQIWNMTWMEWDREINNYTSLIHSLIEE-NH2
791	Ac-ASWSNKSLEQIWNMTWMEWDREINNYTSLIHSLIE-NH2
792	Ac-NASWSNKSLEQIWNMTWMEWDREINNYTSLIHSLI-NH2
793	Ac-WNASWSNKSLEQIWNMTWMEWDREINNYTSLIHSL-NH2

T	No.	Sequence
	793	Ac-WNASWSNKSLEQIWNMTWMEWDREINNYTSLIHSL-NH2
	794	Ac-PWNASWSNKSLEQIWNMTWMEWDREINNYTSLIHS-NH2
	795	Ac-VPWNASWSNKSLEQIWNMTWMEWDREINNYTSLIH-NH2
	796	Ac-AVPWNASWSNKSLEQIWNMTWMEWDREINNYTSLI-NH2
5	797	Ac-TAVPWNASWSNKSLEQIWNMTWMEWDREINNYTSL-NH2
	798	Ac-TTAVPWNASWSNKSLEQIWNMTWMEWDREINNYTS-NH2
	800	Ac-AAASDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
	801	Ac-VFPAAAFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
	802	Ac-VFPSDEAAAASISQVNEKINQSLAFIRKSDELLHNV-NH2
	803	Ac-VFPSDEFDAAAQVNEKINQSLAFIRKSDELLHNV-NH2
	804	Ac-VFPSDEFDASISAAAQVNEKINQSLAFIRKSDELLHNV-NH2
10	805	Ac-VFPSDEFDASISQVNAANQSLAFIRKSDELLHNV-NH2
	806	Ac-VFPSDEFDASISQVNEKIAAALAFIRKSDELLHNV-NH2
	807	Ac-VFPSDEFDASISQVNEKINQSAALAFIRKSDELLHNV-NH2
	808	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
	809	Ac-VFPSDEFDASISQVNEKINQSLAFIRKAAALLHNV-NH2
	810	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDEAAANV-NH2
	811	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLAAA-NH2
15	812	Ac-VYPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
	813	Ac-AAAAIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	814	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	815	Ac-YTSLIHSLIEESQNQQEKQEQELLELDKWASLWNWF-NH2
	816	Ac-QIWNMTWMEWDREINNYTSLIHSLIEESQNQQEKQ-NH2
	817	Ac-QIWNMTWMEWDREINNYTSLIHSLIEESQNQQEKN-NH2
	818	Ac-QIWNMTWMEWDREINNYTSLIHSLIEESQNQQEKQ-NH2
20	819	Ac-NKSLEQIWNMTWMEWDREINNYTSLIHSLIEESQQ-NH2
	820	Ac-FDASISQVNEKINQSLAFIEESDELLHNVNAGKST-NH2
	821	Ac-ACIRKSDELCL-NH2
	823	Ac-YTSLIHSLIEESQNQQEKDEQELLELDKWASLWNWF-NH2
	824	Ac-YTSLIHSLIEESQDQQEKNEQELLELDKWASLWNWF-NH2
	825	Ac-YTSLIHSLIEESQDQQEKDEQELLELDKWASLWNWF-NH2
	826	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWDF-NH2
25	841	Ac-LEANITQSLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	842	Ac-LEANISASLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	843	Ac-LEANISALLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	844	Ac-LEANITALLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	845	Ac-LEANITASLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	845	Ac-LEANITASLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	846	Ac-RAKFKQLLOHYREVAAAKSENDRLRLLLKQMUPS-NH2
30	847	Ac-Abu-DDE-Abu-MNSVKNGTYPKYEEESKLNREIKGVKL-NH2
	856	Ac-WQEWQKVRYLEANISQSLEQAQIQQEKMYELQKL-NH2
	860	Ac-DEYDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
	861	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-NH2

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No.	Sequence
862	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLW-NH2
863	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASL-NH2
864	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWAS-NH2
865	Ac-QARQLLSGIVQQQNNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
5 866	Ac-DREINNYTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
867	Ac-NNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQEELLELDK-NH2
868	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWAAA-NH2
869	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWAAAANWF-NH2
870	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDAAASLWNWF-NH2
871	Ac-YTSLIHSLIEESQNQQEKNEQELLAAAKWASLWNWF-NH2
872	Ac-YTSLIHSLIEESQNQQEKNEQAAAELDKWASLWNWF-NH2
10 873	Ac-YTSLIHSLIEESQNQQEKAAAELLELDKWASLWNWF-NH2
874	Ac-YTSLIHSLIEESQNQAAANEQEELLELDKWASLWNWF-NH2
875	Ac-YTSLIHSLIEESAAAQEKNEQEELLELDKWASLWNWF-NH2
876	Ac-YTSLIHSLIAAAQNQQEKNEQEELLELDKWASLWNWF-NH2
877	Ac-YTSLIHAAAEESQNQQEKNEQEELLELDKWASLWNWF-NH2
878	Ac-YTSAAASLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
879	Ac-EIWNMTWMEWDRENEKINQSLAFIRKSDELLENV-NH2
15 880	Ac-YISEVNEEINQSLAFIRKADELLENVDKWASLWNWF-NH2
881	Ac-TSVITIELSNIKENKANGTDAKVLIKQELDKYKN-NH2
882	YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWFMG-NH2
883	Ac-NEKINQSLAFIRKSDELLENV-NH2
884	Biotin-YDPLVFPSPDEFDASISQVNEKINQSLAFIRKSDEL-NH2
885	Biotin-PLVFPSPDEFDASISQVNEKINQSLAFIRKSDELLH-NH2
886	Biotin-VFPSPDEFDASISQVNEKINQSLAFIRKSDELLENV-NH2
20 887	Biotin-DEFDASISQVNEKINQSLAFIRKSDELLENVNAGK-NH2
888	Biotin-VYPSDEFDASISQVNEKINQSLAFIRKSDELLENV-NH2
889	Biotin-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
890	Ac-VYPSDEFDASISQVQEEIQALAFIRKADELLEQV-NH2
891	Ac-NYTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
892	Ac-NNYTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
893	Ac-INNYTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
25 894	Ac-EINNYTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
895	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWFN-NH2
896	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWFNI-NH2
897	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWFNIT-NH2
898	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWFNITN-NH2
899	Ac-YDPLVFPSPDEFDASISQVNEKINQSLAFIRKSDELLENVNAGK-NH2
900	Ac-NYTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWFN-NH2
30 901	Ac-NNYTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWFNI-NH2
905	Ac-KCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2
906	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2
907	Ac-VYPSDEYDASISQVNEEINQALAYIAADELLENV-NH2

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No.	Sequence
909	Ac-YDASISQVNEEINQALAYIRKADELL-NH2
910	Ac-M-Nle-WMEWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
911	Ac-KNGTYDYPKYEEESKLNREIKGVKLSSMGVYQI-NH2
912	Ac-VTEKIQMASDNINDLIQSGVNTRLTIQSHVQNYI-NH2
5 913	QNQQEKNEQEELLELDKWASLWNWF-NH2
914	Ac-QNQQEKNEQEELLELDKWASLWNWF-NH2
915	LWNWF-NH2
916	ELLELDKWASLWNWF-NH2
917	EKNEQEELLELDKWASLWNWF-NH2
918	SLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
919	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNW
10 920	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWN
921	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLW
922	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASL
923	TSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
924	SLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
925	LIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
926	IHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
15 940	Ac-AAVALLPAVLLALLAPSELEIKRYKNRVASRKCRKFKQLLOHYREVAAAK-NH2
941	Ac-AAVALLPAVLLALLAPCRKFKQLLOHYREVAAAKSSENDRLRLLLKMCP-NH2
942	Ac-YTSLIHSLIEESQNQQEKNNNIEDRWEMWTMNNWIQ-NH2
944	VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
945	Ac-LMQLARQLMQLARQMKQLADSLMQLARQVSRLESA-NH2
946	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQEELL-NH2
947	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
20 948	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
949	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
950	Biotin-W-Nle-EWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
951	Ac-YLEYDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
952	Ac-IKQFINMWQEVGKAMYA-NH2
953	Ac-IRKSDELL-NH2
954	Decanoyl-IRKSDELL-NH2
25 955	Acetyl-Aca-Aca-IRKSDELL-NH2
956	Ac-YDASISQV-NH2
957	Ac-NEKINQSL-NH2
958	Ac-SISQVNEEINQALAYIRKADELL-NH2
959	Ac-QVNEEINQALAYIRKADELL-NH2
960	Ac-EEINQALAYIRKADELL-NH
961	Ac-NQALAYIRKADELL-NH2
30 962	Ac-LAYIRKADELL-NH2
963	FDASISQVNEKINQALAFIRKSDELL-NH2
964	Ac-W-Nle-EWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
965	Ac-ASRKCRKFKQLLOHYREVAAAKSSENDRLRLLLKMCPSLDVDS-NH2

T	No.	Sequence
	967	Ac-WLEWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
	968	Ac-YVKGEPIINFYDPLVFPSEFDASISQVNEKINQSL-NH2
	969	Ac-VYPSDEYDASISQVNEEINQSLAYIRKADELLENV-NH2
	970	Ac-YDASISQVNEEINQALAYIRKADELLENV-NH2
5	971	Ac-YDASISQVNEEINQALAYIRKADELLE-NH2
	972	Ac-VYPSDEYDASISQVNEEINQALAYIRKAAELLENV-NH2
	973	Ac-VYPSDEYDASISQVNEEINQALAYIRKALELLENV-NH2
	974	Decanoyl-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	975	Ac-VYPSDEYDASISQVNEEINQLLAYIRKLDELLENV-NH2
	976	Ac-DEYDASISQVNEKINQSLAFIRKSDELL-NH2
	977	Ac-SNDQSGYAADKESTQKAFDGITNKVNSVIEKTNT-NH2
10	978	Ac-ESTQKAFDGITNKVNSVIEKTNTQFEAVGKEFGNLEKR-NH2
	979	Ac-DGITNKVNSVIEKTNTQFEAVGKEFGNLEKRLENLNK-NH2
	980	Ac-DSNVKNLYDKVRSQLRDNVKELGNGAFEFYHK-NH2
	981	Ac-RDNVKELGNGAFEFYHKADDEALNSVKNGTYDYPKY-NH2
	982	Ac-EFYHKADDEALNSVKNGTYDYPKY-NH2
	983	Ac-AAVALLPAVLLALLAPAADKESTQKAFDGITNKVNS-NH2
	984	Ac-AAVALLPAVLLALLAPAADSNVKNLYDKVRSQLRDN-NH2
15	985	Ac-KESTQKAFDGITNKVNSV-NH2
	986	Ac-IEKTNTQFEAVGKEFGNLER-NH2
	987	Ac-RLENLNKRVEDGFLDVWTYNAELLVALENE-NH2
	988	Ac-SNVKNLYDKVRSQLRDN-NH2
	989	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQEEL-NH2
	990	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
	991	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQEEL-NH2
20	992	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
	993	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
	994	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEELL-NH2
	995	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEEL-NH2
	996	Ac-YTKFIYTLLEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	997	Ac-YMKQLADSLMQLARQVSRLESA-NH2
	998	Ac-YLMQLARQMQLADSLMQLARQVSRLESA-NH2
25	999	Ac-YQEWERKVDPLEENITALLEEAIQQEKNMYELQKL-NH2
	1000	Ac-WMAWAAAINNYTSLIHSLIEESQNQQEKNEQEEL-NH2
	1001	Ac-YASLIAALIEESQNQQEKNEQEELLELAKWAALWAF-NH2
	1002	[Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEGGC-NH2] dimer
	1003	Ac-YDISIELNKAUSDLEESKEWIKKSNQKLDSIGNWH-NH2
	1004	Biotinyl-IDISIELNKAUSDLEESKEWIKKSNQKLDSIGNWH-NH2
	1005	Ac-YTSLI-OH
30	1006	Fmoc-HSLIEE-OH
	1007	Fmoc-SQNQQEK-OH
	1008	Fmoc-NEQEELLE-OH
	1009	Fmoc-DKWASL-OH

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No.	Sequence
1010	Fmoc-WNWF-OH
1011	Ac-AKTLERTWDTLNHLLFISSALYKLNKLSVAQITLSI-NH2
1012	Ac-NITLQAKIKQFINMWQEVGKAMYA-NH2
1013	Ac-LENERTLDFHDSNVKNLYDKVRLQLRDN-NH2
5 1014	Ac-LENERTLDFHDSNVKNLYDKVRLQLRDNVKELGNG-NH2
1015	Ac-TLDFHDSNVKNLYDKVRLQLRDNVKELGNGAFEF-NH2
1016	Ac-IDISIELNKAUSDLEESKEWIKKSNQKLD SIGNWH-NH2
1021	Biotinyl-SISQVNEEINQALAYIRKADELL-NH2
1022	Biotinyl-SISQVNEEINQSLAYIRKSDELL-NH2
1023	Ac-SISQVNEEINQSLAYIRKSDELL-NH2
1024	Ac-IDISIELNKAUSDLEESKEWIEKSNQELD SIGNWE-NH2
10 1025	Ac-IDISIELNKAUSDLEESKEWIKKSNQELD SIGNWH-NH2
1026	Ac-IDISIELNKAUSDLEEAKEWIDDANQKLD SIGNWH-NH2
1027	Ac-IDISIELNKAUSDLEESKEWIKKANQKLD SIGNWH-NH2
1028	Ac-IDISIELNKAUSDLEEAKEWIKKSNQKLD SIGNWH-NH2
1029	Biotinyl-NSVALDPIDISIELNKAUSDLEESKEWIKKSNQKL-NH2
1030	Biotinyl-ALDPIDISIELNKAUSDLEESKEWIKKSNQKLD SI-NH2
1031	desAminoTyrosine-NSVALDPIDISIELNKAUSDLEESKEWIKKSNQKL-NH2
15 1032	desAminoTyrosine-ALDPIDISIELNKAUSDLEESKEWIKKSNQKLD SI-NH2
1033	Ac-YDASISQVNEEINQALAFIRKADEL-NH2
1034	Ac-YDASISQVNEEINQSLAYIRKADELL-NH2
1035	Biotinyl-YDASISQVNEEINQALAYIRKADELL-NH2
1036	Biotinyl-YDASISQVNEEINQSLAFIRKSDELL-NH2
1037	Ac-YDASISQVNEEINQSLAFIRKSDELL-NH2
1038	Ac-WLEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
20 1039	Biotinyl-IDISIELNKAUSDLEESKEWIRRSNQKLD SIGNWH-NH2
1044	Ac-YESTQKAFDGITNKVNSVIEKTINTQFEAVGKEFGNLEKR-NH2
1045	Biotin-DEYDASISQVNEKINQSLAFIRKSDELL-NH2
1046	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
1047	Ac-WQEWQKVRYLEANISQSLEQAQIQQEKKNMYEL-NH2
1048	Ac-WQEWQKVRYLEANISQSLEQAQIQQEKNEYEL-NH2
1049	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYEL-NH2
25 1050	Ac-WQEWQKVRYLEANITALLEQAQIQQEKKNMYEL-NH2
1051	Ac-WQEWQKVRYLEANISQSLEQAQIQQEKNEYELQKL-NH2
1052	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1053	Ac-WQEWQKVRYLEANITALLEQAQIQQEKKNMYELQKL-NH2
1054	Ac-IDISIELNKAUSDLEESKEWIEKSNQKLD SIGNWH-NH2
1055	Ac-EFGNLEKRLENLNKRVEDGFLDVWTYNAELLVALENE-NH2
1056	Ac-EDGFLDVWTYNAELLVLMENERTLDFHDSNVKNLYDKVQMQL-NH2
30 1057	Ac-SISQVNEKINQSLAFIRKSDELL-NH2
1058	desaminoTyr-SISQVNEKINQSLAFIRKSDELL-NH2
1059	Ac-SISQVNEKINQSLAYIRKSDELL-NH2
1060	Ac-QQLLDVVKRQQEMLRLTVWGTKNLQARVTAIEKYLKDQ-NH2

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No.	Sequence
1061	YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWFC
1062	Ac-FDASISQVNEKINQSLAYIRKSDELL-NH2
1063	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWA
1064	Indole-3-acetyl-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
5 1065	Indole-3-acetyl-DEFDESISQVNEKINQSLAFIRKSDELL-NH2
1066	Indole-3-acetyl-DEFDESISQVNEKIEQSLAFIRKSDELL-NH2
1067	Indole-3-acetyl-DEFDESISQVNEKIEESLAFIRKSDELL-NH2
1068	Indole-3-acetyl-DEFDESISQVNEKIEESLQFIRKSDELL-NH2
1069	Indole-3-acetyl-GGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1070	2-Napthoyl-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
1071	desNH2Tyr-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
10 1072	biotin-ALDPIDISIELNKAASDLEESKEWIRRSNQKLDI-NH2
1073	Ac-YDASISQVNEKINQALAYIRKADELHNVNAGKST-NH2
1074	Ac-VYPSDEYDASISQVNEKINQALAYIRKADELHNV-NH2
1075	Ac-VYPSDEYDASISQVNEKINQSLAYIRKSDELHNV-NH2
1076	Ac-WGWGYGYG-NH2
1077	Ac-YGWGWGWGF-NH2
1078	Ac-WQEWQKVRYLEANITALQEQAQIAEKAIEYELQKL-NH2
15 1079	Ac-WQEWQKVRYLEAEITALQEQAQIAEKAIEYELQKL-NH2
1081	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKAS
1082	Ac-VWPSDEFDASISQVNEKINQSLAFIRKSDELHNV-NH2
1083	Ac-SKNISEQIDQIKKDEQKEGTGWLGGKWWTSDWGV-NH2
1084	Ac-LSKNISEQIDQIKKDEQKEGTGWLGGKWWTSDWG-NH2
1085	Ac-DLSKNISEQIDQIKKDEQKEGTGWLGGKWWTSDW-NH2
1086	Ac-EDLSKNISEQIDQIKKDEQKEGTGWLGGKWWTSD-NH2
20 1087	Ac-IEDLSKNISEQIDQIKKDEQKEGTGWLGGKWWTS-NH2
1088	Ac-GIEDLSKNISEQIDQIKKDEQKEGTGWLGGKWWT-NH2
1089	Ac-IGIEDLSKNISEQIDQIKKDEQKEGTGWLGGKWW-NH2
1090	2-Napthoyl--PSDEFDASISQVNEKINQSLAFIRKSDELHNV-NH2
1091	Ac-VYPSDEYDASISQVNEKINQALAYIRKADELLENV-NH2
1092	Ac-VYPSDEFDASISQVNEKINQALAFIRKADELLENV-NH2
1093	Ac-VYPSDEYDASISQVNEKINQALAYIREADELLENV-NH2
25 1094	Biotinyl-YDASISQVNEKINQSLAFIRESDELL-NH2
1095	Ac-AIGIEDLSKNISEQIDQIKKDEQKEGTGWLGGKW-NH2
1096	Ac-AAIGIEDLSKNISEQIDQIKKDEQKEGTGWLGGK-NH2
1097	Ac-DAAIGIEDLSKNISEQIDQIKKDEQKEGTGWLGG-NH2
1098	Ac-PDAAIGIEDLSKNISEQIDQIKKDEQKEGTGWLGG-NH2
1099	Ac-NITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQWI-NH2
1100	Ac-KNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQW-NH2
30 1101	Ac-TKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQ-NH2
1102	Ac-WTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWR-NH2
1103	Ac-DWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGW-NH2
1104	Ac-HDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTG-NH2

T	No.	Sequence
	1105	Ac-PHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWT-NH2
	1106	Ac-EPHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWW-NH2
	1107	Ac-IEPHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWW-NH2
	1108	Ac-AIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDNDN-NH2
5	1109	Ac-AAIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDND-NH2
	1110	Ac-DAAIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDND-NH2
	1111	Ac-LSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPIFF-NH2
	1112	Ac-GLSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPIF-NH2
	1113	Ac-VGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPI-NH2
	1114	Ac-FVGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLL-NH2
	1115	Ac-WFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLL-NH2
10	1116	Ac-QWFVFLSPTVWLSVIWMMWYWGPSLYSILSPFLPL-NH2
	1117	Ac-VQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLP-NH2
	1118	Ac-FVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFL-NH2
	1119	Ac-PFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPF-NH2
	1120	Ac-VPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSP-NH2
	1121	Ac-LVPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILS-NH2
	1122	H-NHTTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKW-OH
15	1123	H-QARQLLSGIVQQQNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-OH
	1124	Ac-VYPSDEFDASISQVNEKINQSLAFIREADELLENV-NH2
	1125	Ac-VFPSDEFDASISQVNEKINQSLAYIREADELLENV-NH2
	1126	Ac-DEFDASISQVNEKINQSLAYIREADELL-NH2
	1127	Ac-NEQELLELDKWASLWNWFGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
	1128	Ac-LELDKWASLWNWFGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
	1129	Naphthoyl-EGEGEGEGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
20	1130	Ac-ASRKCRKFKQLLQHYREVAAAKSENDRLRLLLLKQMCPSLDV-NH2
	1131	Naphthoyl-GDEEDASISQVNEKINQSLAFIRKSDELL-NH2
	1132	Naphthoyl-GDEEDASESQVNEKINQSLAFIRKSDELL-NH2
	1133	Naphthoyl-GDEEDASESQNEKINQSLAFIRKSDELL-NH2
	1134	Naphthoyl-GDEEDASESQNEKQNSLAFIRKSDELL-NH2
	1135	Naphthoyl-GDEEDASESQNEKQNSLAFIRKSDELL-NH2
	1136	Ac-WGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
25	1137	Ac-YTSLGGDEFDESISQVNEKIEESLAFIRKSDELLGGWNWF-NH2
	1138	Ac-YTSLIHSLLGGDEFDESISQVNEKIEESLAFIRKSDELLGGWASLWNWF-NH
	1139	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIRKSDELL-NH2
	1140	2-Naphthoyl-GDEEDESISQVNEKIEESLAFIRKSDELL-NH2
	1141	2-Naphthoyl-GDEEDESISQVQEKIEESLAFIRKSDELL-NH2
	1142	2-Naphthoyl-GDEEDESISQVQEKIEESLLFIRKSDELL-NH2
	1143	Biotin-GDEYDESISQVNEKIEESLAFIRKSDELL-NH2
30	1144	2-Naphthoyl-GDEYDESISQVNEKIEESLAFIRKSDELL-NH2
	1145	Ac-YTSLIHSLLIDEQEKIEELAFIRKSDELLELDKWNWF-NH2
	1146	VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	1147	Ac-NNLLRAIEAQHLLQLTVWGSKQLQARILAVERYLKDQ-NH2

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No.	Sequence
1148	GGGVYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1149	Ac-NNLLRAIEAQHLLQLTVWGEKQLQARILAVERYLKDQ-NH2
1150	Ac-PTRVNYILIIGVLVLAbuEVTGVRADVHLL-NH2
1151	Ac-PTRVNYILIIGVLVLAbuEVTGVRADVHLLLEQPGNLW-NH2
5 1152	Ac-PEKTPLLPTRVNYILIIGVLVLAbuEVTGVRADVHLL-NH2
1153	AhaGGGVYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1155	Ac-YTSLIHSLGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1156	Ac-YTSLGGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1157	Ac-DEFDESISQVNEKIEESLAFIRKSDELLGGWASLWNWF-NH2
1158	Ac-DEFDESISQVNEKIEESLAFIRKSDELLGGWNWF-NH2
1159	Ac-YTSLIHSLEESQNQQEKNEQELLELDKASLWNWF-NH2
10 1160	Ac-YTSLIHSLEESQNQQEKNEQELLELDKSLWNWF-NH2
1161	Ac-YTSLIHSLEESQNQQEKNEQELLELDKLWNWF-NH2
1162	Ac-YTSLIHSLEESQNQQEKNEQELLELDKWNWF-NH2
1163	Ac-MTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKASLWNWF-NH2
1164	Ac-MTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKSLWNWF-NH2
1165	Ac-MTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKLWNWF-NH2
1166	Ac-MTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKWNWF-NH2
15 1167	Ac-MTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKASLWN-NH2
1168	Ac-MTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKASL-NH2
1169	(Pyr)HWSY(2-naphthyl-D-Ala)LRPG-NH2
1170	Ac-WNWFDEFDESISQVNEKIEESLAFIRKSDELLWNWF-NH2
1171	Ac-YTSLIHSLEESQNQQEKNEQELLELDKYASLYNYF-NH2
1172	Ac-YTSLIHSLEESQNQQEKNEQELLELDKYAYLYNYF-NH2
1173	2-Naphthoyl-AcaAcaAcaDEFDESISQVNEKIEESLAFIRKSDELLAcaAcaAcaW-NH2
20 1174	2-Naphthoyl-AcaAcaAcaGDEFDESISQVNEKIEESLAFIRKSDELLGacaAcaAcaW-NH2
1175	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIRESDELL-NH2
1176	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIEESDELL-NH2
1177	Ac-WQEWQKVNYLEANITALLEQAQIQQEKNEYELQKL-NH2
1178	Ac-WQEWQKVDYLEANITALLEQAQIQQEKNEYELQKL-NH2
1179	Ac-WQEWQKVRWLEANITALLEQAQIQQEKNEYELQKL-NH2
1180	Ac-WQEWQQVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
25 1181	Ac-WQEWQVRYRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1182	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1183	Ac-WQEWQVRYRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1184	Ac-WQEWQVRYRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1185	Ac-WQEWQVRYRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1186	Ac-WQEWQKVRYRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1187	Ac-WQEWQKVRFLLEANITALLEQAQIQQEKNEYELQKL-NH2
30 1188	Ac-VNalPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1189	Ac-VNalPSDENalDASISQVNEEINQALAYIRKADELLENV-NH2
1190	Ac-VNalPSDEYDASISQVNEEINQALANalIRKADELLENV-NH2
1191	Ac-VYPSDEFDASISQVNEKINQSLAFIREADELLFNFF-NH2

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No.	Sequence
1192	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLFNFF-NH2
1193	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1194	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1195	Ac-YTSLITALLEQAQIQQEKNEYELQKLDEWASLWEWF-NH2
5 1196	Ac-YTSLITALLEQAQIQQEKNEYELQELDEWASLWEWF-NH2
1197	Ac-YTSLITALLEEAQIQQEKNEYELQELDEWASLWEWF-NH2
1198	Naphthoyl-Aua-Aua-Aua-TALLEQAQIQQEKNEYELQKLAua-Aua-Aua-W-NH2
1199	Ac-WAAWEQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1200	Ac-WQEAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1201	Ac-WQEWAAKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1202	Ac-WQAAEQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
10 1203	Ac-WQEWAAVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1204	Ac-WQEWQAARYLEANITALLEQAQIQQEKNEYELQKL-NH2
1205	Ac-WQEWQKAAYLEANITALLEQAQIQQEKNEYELQKL-NH2
1206	Ac-WQEWQKVALEANITALLEQAQIQQEKNEYELQKL-NH2
1207	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKLGGGGWASLWNF-NH2
1208	2-Naphthoyl-GDEFDASISQVNEKINQSLAFIRKSDELTA-NH2
1209	2-Naphthoyl-GDEFDASISQVNEKINQSLAFTRKSDELTA-NH2
15 1210	2-Naphthoyl-GDEFDASISQVNEKTNQSLAFTRKSDELTA-NH2
1211	2-Naphthoyl-GDEFDASISQVNEKTNQSLAFTRKSDELTA-NH2
1212	2-Naphthoyl-GDEFDASTSQTNEKTNQSLAFTRKSDELTA-NH2
1213	2-Naphthoyl-GDEYDASTSQTNEKTNQSLAFTRKSDELTA-NH2
1214	2-Naphthoyl-GDEFDEEISQVNEKIEESLAFIRKSDELL-NH2
1215	2-Naphthoyl-GDEFDASISQVNEKINQSLAFIRKSDELA-NH2
1216	2-Naphthoyl-GDEFDASASQANEKANQSLAFARKSDELA-NH2
20 1217	2-Naphthoyl-GDEFDESISQVNEKIEESLAFTRKSDELL-NH2
1218	2-Naphthoyl-GDEFDESISQVNEKTEESLAFIRKSDELL-NH2
1219	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1220	2-Naphthoyl-GDEFDESTSQTNEKIEESLAFIRKSDELL-NH2
1221	Ac-WNWFDEFDESTSQTNEKIEESLAFIRKSDELLWNWF-NH2
1222	Ac-WNWFDEFDESTSQTNEKIEESLAFIRKSDELLWNWF-NH2
1223	Ac-WNWFDEFDESTSQTNEKTEESLAFIRKSDELLWNWF-NH2
25 1224	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVAL-NH2
1225	Ac-YTNLIYTLLEESQNQQEKNEQELLELDKWASLWSWF-NH2
1226	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1227	Ac-NNMTWQEWQKVRYLEANITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1230	Ac-WNWFIEESDELLWNWF-NH2
1231	2-Naphthoyl-GFIEESDELLW-NH2
1232	Ac-WFIEESDELLW-NH2
30 1233	2-Naphthoyl-GFNFFIEESDELLFNFF-NH2
1234	2-Naphthoyl-GESDELW-NH2
1235	Ac-WNWFDEFDESISQVQEEIEESLAFIEESDELLGGWNWF-NH2
1236	Ac-WNWFHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2

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No.	Sequence
1237	Ac-YTSLITALLEQAQIQQEENEYELQALDEWASLWETF-NH2
1238	Ac-YTSLIHSLGGDEFDESISQVNEEIEESLAFIEESDELLGGWASLWETF-NH2
1239	2-Naphthoyl-GDEFDESISQVQEEIEESLAFIEESDELL-NH2
1240	H-QARQLSSIMQQQNNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-OH
5	1241 Ac-CPKYVKQNTLKLATGMRNVPEKQTR-NH2
	1242 Ac-GLFGAIAAGFIENGWEGMIDGWYGFRRHNSC-NH2
	1243 Ac-LNFLGGT-NH2
	1244 Ac-LDSWWTSLNFLGGT-NH2
	1245 Ac-ILTIPQSLDSWWTSLNFLGGT-NH2
	1246 Ac-GFFLLTRILTIPOSLDSWWTSLNFLGGT-NH2
	1247 Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKASLWETF-NH2
10	1248 Ac-WNWFITALLEQAQIQQEKNEYELQKLDKASLWETF-NH2
	1249 Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKASLWETF-NH2
	1250 Ac-WQEWQKVRYLEANITALLEQAQIQQEKIEYELQKL-NH2
	1251 Ac-WQEWQKVRYLEAQITALLEQAQIQQEKIEYELQKL-NH2
	1252 Ac-KENKANGTDAKVLIKQELDKYKNAVTELQLLMQS-NH2
	1253 Ac-NIKENKANGTDAKVLIKQELDKYKNAVTELQLLM-NH2
	1254 (FS) -YTSLIHSLIEESQNQQEKNEQELLELDKASLWETF-NH2
15	1255 2-Naphthoyl-GWNWFAcaDEFDESISQVQEEIEESLAFIEESDELLAcaWNWF-NH2
	1256 Ac-WNWFDEFDESISQVNEKIEESLAFIEESDELLGWNWF-NH2
	1257 Ac-WNWFDEFDESISQVNEKIEESLAFIRKSEDELLGWNWF-NH2
	1258 Ac-WNWF-Aca-DEFDESISQVNEKIEESLAFIRKSEDELL-Aca-WNWF-NH2
	1259 Ac-WNWF-Aca-DEFDESISQVNEKIEESLAFIEESDELL-Aca-WNWF-NH2
	1260 Ac-EESQNQQEKNEQELLELDKWA-NH2
	1261 EESQNQQEKNEQELLELDKWA
20	1262 Ac-CGTTDRSGAPTYSWGANDTDVFLNNTRPPLGNWFG-NH2
	1263 Ac-GVEHRLEAACNWTRGERADLEDRDRSELSP-NH2
	1264 Ac-CVREGNASRAWAVTPTVATRDGKLPT-NH2
	1265 Ac-CFSPRHHWTTQDANASIYPG-NH2
	1266 Ac-LQHYREVAAKSSENDRLRLLKQMCPSLDVDS-NH2
	1267 Ac-WQEWDRISNYTSLITALLEQAQIQQEKNEYELQKLDWASLWETF-NH2
	1268 Ac-CWQEWDRISNYTSLITALLEQAQIQQEKNEYELQKLDWASLWETF-NH2
25	1269 Ac-WQEWDRISNYTSLITALLEQAQIQQEKNEYELQKLDWETF-NH2
	1270 Ac-CWQEWDRISNYTSLITALLEQAQIQQEKNEYELQKLDWETF-NH2
	1271 Ac-GQNSQSPTSNSHPTSAPPTAPGYRWA-NH2
	1272 Ac-PGSSTTSTGPARTALTTAQGTSLYPSA-NH2
	1273 Ac-PGSSTTSTGPARTALTTAQGTSLYPSAAATKPSDGNATA-NH2
	1275 Ac-WQEWDRITALLEQAQIQQEKNEYELQKLDKASLWETF-NH2
	1276 Ac-WQEWDRITALLEQAQIQQEKNEYELQKLDWASLWETF-NH2
30	1277 Ac-WQEWDRITALLEQAQIQQEKNEYELQKLDWETF-NH2
	1278 Ac-WQEWDRITALLEQAQIQQEKNEYELQKLDWETF-NH2
	1279 Ac-WQEWREITALLEQAQIQQEKNEYELQKLIEWETF-NH2
	1280 Ac-WQEWREITALLEQAQIQQEKIEYELQKLDWETF-NH2

T	No.	Sequence
	1281	Ac-WQEWEITALLEQAQIQQEKNEYELQKLDEWEWF-NH2
	1282	Ac-WQEWEITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
	1283	Ac-WQEWEITALLEQAQIQQEKIEYELQKLDEWEWF-NH2
	1284	Ac-WQEWEITALLEQAQIQQEKIEYELQKLIEWEWF-NH2
5	1285	Ac-WQEWREIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
	1286	Ac-WQEWEREIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
	1287	Ac-WQEWEIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
	1288	Ac-WQEWREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1289	Ac-WQEWEREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1290	Ac-WQEWEIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1291	Ac-WQEWDEYDASISQVNEKINQALAYIREADELWEWF-NH2
10	1292	Ac-WQEWDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1293	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIEWEWF-NH2
	1294	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIEWASLWEWF-NH2
	1295	Ac-WQEWEITALLEQAQIQQEKIEYELQKLIEWASLWEWF-NH2
	1298	-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	1299	Ac-WVYPSDEYDASISQVNEEINQALAYIRKADELLENVWNWF-NH2
	1300	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
15	1301	Ac-WQEWDEYDASISQVNEKINQALAYIREADELWAWF-NH2
	1302	Ac-WQAWDEYDASISQVNEKINQALAYIREADELWAWF-NH2
	1303	Ac-WQAWDEYDASISQVNEKINQALAYIREADELWEWF-NH2
	1304	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-NH2
	1305	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAF-NH2
	1306	Biotin-QVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
	1307	Ac-WMEWDREI-NH2
20	1308	Ac-WQEWEQKI-NH2
	1309	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIKWASLWEWF-NH2
	1310	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIEWASLWEWF-NH2
	1311	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKLIEWEWF-NH2
	1312	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKEWEWF-NH2
	1313	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKEWEW-NH2
	1314	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKLIEWEW-NH2
25	1315	Ac-FNLSDHSESIQKKFQLMKKHVNKIGVSDPIGSWLR-NH2
	1316	Ac-DHSESIQKKFQLMKKHVNKIGVSDPIGSWLRGIF-NH2
	1317	Ac-WSVKQANLTTSLLDLLDDVTSIRHAVLQNRA-NH2
	1318	Biotin-WMEWDREI-NH2
	1319	Biotin-NNMTWMEWDREINNYTSL-NH2
	1320	Ac-GAASLTTLTVQARQLLSGIVQQQNLLRAIEAQQHLL-NH2
	1321	Ac-ASLTTLTVQARQLLSGIVQQQNLLRAIEAQQHLLQL-NH2
30	1322	Ac-VSVGNTLYYVVKQEGKSLYVKGEPIINFYDPLVF-NH2
	1323	Ac-QHWSYGLRPG-NH2
	1324	Ac-WQEWEQKIQHWSYGLRPGWASLWEWF-NH2
	1325	Ac-WQEWEQKIQHWSYGLRPGWEWF-NH2

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No.	Sequence
1326	Ac-WNWFQHWSYGLRPGWNWF-NH2
1327	Ac-FNFFQHWSYGLRPGFNFF-NH2
1328	Ac-GAGAQHWSYGLRPGAGAG-NH2
1329	PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT
5	1330 Ac-WQWEQKITALLEQAQIQQEKIEYELQKLAKWASLWEWF-NH2
	1331 Ac-WQWEQKITALLEQAQIQQEKIEYELQKLAEWASLWEWF-NH2
	1332 Ac-WQWEQKITALLEQAQIQQEKAEYELQKLAEWASLWEWF-NH2
	1333 Ac-WQWEQKITALLEQAQIQQEKAEYELQKLAEWASLWAWF-NH2
	1334 Ac-WQWEQKITALLEQAQIQQEKAEYELQKLAKWASLWAWF-NH2
	1335 Ac-TNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPVVK-NH2
	1336 Ac-KAVVSLSNGVSVLTSKVLDLKNYIDKQLLPVVKQS-NH2
10	1337 Ac-WQWEQKITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
	1338 Ac-WQWEQKITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
	1339 Ac-WQWEQKITALLEQAQIQQEKIEYELQKLDKWEWF-NH2
	1340 Ac-YDPLVFPSPDEFDASISQVNEKINQSLAF-NH2
	1341 Fluor--VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	1342 Fluor-YTSLIHSLIEESQNNQEQEKNEQELLELDKWASLWNWF-NH2
	1344 Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARIL-NH2
15	1345 Ac-QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	1346 Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	1347 Ac-WQWEQKITALLEQAQIQQEKNEYELQKLAEWASLWAWF-NH2
	1348 Ac-WQWEQKITALLEQAQIQQEKNEYELQKLAEWASLWAW-NH2
	1349 Ac-WQWEQKITALLEQAQIQQEKAEYELQKLAEWASLWAW-NH2
	1350 Ac-WQWEQKITALLEQAQIQQEKNEYELQKLAEWAGLWAWF-NH2
	1351 Ac-WQWEQKITALLEQAQIQQEKNEYELQKLAEWAGLWAW-NH2
20	1352 Ac-WQWEQKITALLEQAQIQQEKAEYELQKLAEWAGLWAW-NH2
	1353 Ac-WQWEQKITALLEQAQIQQEKNEYELQKLDKWAGLWEWF-NH2
	1354 Ac-WQEWQHWSYGLRPGWEWF-NH2
	1355 Ac-WQAWQHWSYGLRPGWAWF-NH2
	1356 Biotinyl-WQWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
	1357 WQWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF
	1358 WQWEQKITALLEQAQIQQEKIEYELQKLIEWEWF
25	1361 Ac-AGSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQ-NH2
	1362 Ac-AGSAMGAASLTLSAQSRRTLLAGIVQQQQQLLDVVKRQQ-NH2
	1363 Ac-AGSAMGAASTALTAQSRRTLLAGIVQQQQQLLDVVKRQQ-NH2
	1364 Ac-ALTAQSRRTLLAGIVQQQQQLLDVVKRQQELLRLTVWGT-NH2
	1365 Ac-TLSAQSRRTLLAGIVQQQQQLLDVVKRQQEMLRLTVWGT-NH2
	1366 Ac-TLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGI-NH2
	1367 Ac-WQAWIEYEASLSQVKEKIEQSLAYIREADELWAWF-NH2
30	1368 Ac-WQAWIEYEASLSQAKEKIEESKAYIREADELWAWF-NH2
	1369 Ac-WQAWIEYERLLVQAKLKIAIAKLYIAKELLEWAWF-NH2
	1370 Ac-WQAWIEYERLLVQVKLKIAIAKLYIAKELLEWAWF-NH2
	1371 Ac-WQAWIELERLLVQVKLKIAIAKLEIAKELLEWAWF-NH2

T	No.	Sequence
	1372	Ac-GEWTYDDATKTFTVTEGGH-NH2
	1373	Ac-WQEWQKIGEWTYDDATKTFTVTEGGHWASLWEWF-NH2
	1374	Ac-GEWTYDDATKTFTVTE-NH2
	1375	Ac-WQEWQKIGEWTYDDATKTFTVTEWASLWEWF-NH2
5	1376	Ac-MHRFDYRT-NH2
	1377	Ac-WQEWQKIMHRFDYRTWASLWEWF-NH2
	1378	Ac-MHRFNWSTGGG-NH2
	1379	Ac-WQEWQKIMHRFNWSTGGGWASLWEWF-NH2
	1380	Ac-MHRFNWST-NH2
	1381	Ac-WQEWQKIMHRFNWSTWASLWEWF-NH2
	1382	Ac-LLVPLARIMTMSSVHGGG-NH2
10	1383	Ac-WQEWQKILLVPLARIMTMSSVHGGGWASLWEWF-NH2
	1384	Ac-LLVPLARIMTMSSVH-NH2
	1385	Ac-WQEWQKILLVPLARIMTMSSVHWASLWEWF-NH2
	1386	TALLEQAQIQQEKNEYELQKLDK
	1387	Ac-TALLEQAQIQQEKNEYELQKLDK-NH2
	1388	Ac-TALLEQAQIQQEKIEYELQKLIE-NH2
	1389	TALLEQAQIQQEKIEYELQKLIE
15	1390	Ac-QARQLLSGIVQQNNLLRAIEAQHLLQLTVWGIKQLQARILAVERY-NH2
	1391	Rhod-QARQLLSGIVQQNNLLRAIEAQHLLQLTVWGIKQLQARILAVERY-NH2
	1392	Ac-GAASLTLSAQSRITLLAGIVQQQQQLLDVVKRQQEML-NH2
	1393	Ac-GSAMGAASLTLSAQSRITLLAGIVQQQQQLLDVVKRQQEML-NH2
	1394	Ac-PALSTGLIHLHQNIVDVQFLFGVGSSIASWAIKWEY-NH2
	1395	Ac-PALSTGLIHLHQNIVDVQFLYGVGSSIASWAIK-NH2
	1396	Ac-LSTTQWQVLPUSFTTLPALSTGLIHLHQNIVDVQY-NH2
20	1397	Ac-FRKFPEATFSRUGSGPRITPRUMVDFPFRLWHY-NH2
	1398	Ac-DPPFRLWHFPUTINYTIFKVRLFVGGVEHRLEAAUNWTR-NH2 <sup>σ</sup>
	1399	Ac-YVGGVEHRLEAAUNWTRGERUDLEDRDRSELSPL-NH2
	1400	MVYPSDEYDASISQVNEEINQALAYIRKADELLENV
	1402	Ac-GPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGG-NH2
	1403	Ac-LGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLG-NH2
	1404	Ac-FLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFL-NH2
25	1405	Ac-YTNTIYTLLEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	1406	YTNTIYTLLEESQNQQEKNEQEELLELDKWASLWNWF
	1407	Ac-YTGIIYNLLEESQNQQEKNEQEELLELDKWANLWNWF-NH2
	1408	YTGIIYNLLEESQNQQEKNEQEELLELDKWANLWNWF
	1409	Ac-YTSLIYSLLEKSQIQQEKNEQEELLELDKWASLWNWF-NH2
	1410	YTSLIYSLLEKSQIQQEKNEQEELLELDKWASLWNWF
	1411	Ac-EKSQIQQEKNEQEELLELDKWA-NH2
30	1412	EKSQIQQEKNEQEELLELDKWA
	1413	Ac-EQAQIQQEKNEYELQKLDKWA-NH2
	1414	Ac-YTSLIGSLIEESQIQQERNEQEELLELDKWASLWEWF-NH2
	1415	Ac-YTXLIHSLIXESQNQQXKNEQELXELDKWASLWNWF-NH2

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No.	Sequence
1416	Ac-YTXLIHSLIWESQNQQXKNEQELXELD-NH2
1417	Ac-YTSLIHSLIEESQNQQEKNEQELLELD-NH2
1418	Ac-WQEQEXKITALLXQAQIQQXKNEYELXKLDKWASLWEWF-NH2
1419	Ac-XKITALLXQAQIQQXKNEYELXKLDKWASLWEWF-NH2
5 1420	Ac-WQEWXKITALLXQAQIQQXKNEYELXKLD-NH2
1421	Ac-WEQKITALLEQAQIQQEKNEYELQKLD-NH2
1422	Ac-WEXKITALLXQAQIQQXKNEYELXKLD-NH2
1423	Ac-XKITALLXQAQIQQXKNEYELXKLD-NH2
1425	Ac-QKITALLEQAQIQQEKNEYELQKLD-NH2
1426	Ac-QKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1427	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLD-NH2
10 1428	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLEN-OH
1429	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLE-OH
1430	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELL-OH
1431	Ac-VYPSDEYDASISQVNEEINQALAYIRKADEL-OH
1432	YPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1433	PSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1434	SDEYDASISQVNEEINQALAYIRKADELLENV-NH2
15 1435	DEYDASISQVNEEINQALAYIRKADELLENV-NH2
1436	Ac-VYPSDEYDASISQVDEEINQALAYIRKADELLENV-NH2
1437	Ac-VYPSDEYDASISQVNEEIDQALAYIRKADELLENV-NH2
1438	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLEDV-NH2
1439	Ac-VYPSDEYDASISQVDEEIDQALAYIRKADELLENV-NH2
1440	Ac-LLSTNKAVVSLSNGVSVLTSTKVLDLKNYIDKQLLP-NH2
1441	Ac-LSTNKAVVSLSNGVSVLTSTKVLDLKNYIDKQLLP I-NH2
20 1442	Ac-STNKAVVSLSNGVSVGTSTKVLDLKNYIDKQLLP IV-NH2
1443	Ac-TNKAVVSLSNGVSVLTSTKVLDLKNYIDKQLLP IVN-NH2
1444	Ac-NKAVVSLSNGVSVLTSTKVLDLKNYIDKQLLP IVNK-NH2
1445	Ac-KAVVSLSNGVSVLTSTKVLDLKNYIDKQLLP IVNKQ-NH2
1446	Ac-AVVSLSNGVSVLTSTKVLDLKNYIDKQLLP IVNKQS-NH2
1447	Ac-VVSLSNGVSVLTSTKVLDLKNYIDKQWLLPIV NKQSU-NH2
1448	Ac-VSLSNGVSVLTSTKVLDLKNYIDKQLLP IVNKQSUS-NH2
25 1449	Ac-SLSNGVSVLTSTKVLDLKNYIDKQLLP IVNKQSUSI-NH2
1450	Ac-LSNGVSVLTSTKVLDLKNYIDKQLLP IVNKQSUSIS-NH2
1451	Ac-SNGVSVLTSTKVLDLKNYIDKQLLP IVNKQSUSISN-NH2
1452	Ac-NGVSVLTSTKVLDLKNYIDKQLLP IVNKQSUSISNI-NH2
1453	Ac-GVSVLTSTKVLDLKNYIDKQLLP IVNKQSUSISNIE-NH2
1454	Ac-VSVLTSTKVLDLKNYIDKQLLP IVNKQSUSISINIET-NH2
1455	Ac-SVLTSTKVLDLKNYIDKQLLP IVNKQSUSISNIETV-NH2
30 1456	Ac-VLTSTKVLDLKNYIDKQLLP IVNKQSUSISNIETVI-NH2
1457	Ac-LTSKVLDLKNYIDKQLLP IVNKQSUSISNIETVIE-NH2
1458	Ac-TSKVLDLKNYIDKQLLP IVNKQSUSISNIETVIEF-NH2
1459	Ac-SKVLDLKNYIDKQLLP IVNKQSUSISNIETVIEFQ-NH2

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No.	Sequence
1460	Ac-KVLDLKNYIDKQLLPVKNQSSUSISNIETVIEFQQ-NH2
1461	Ac-VLDLKNYIDKQLLPVKNQSSUSISNIETVIEFQQK-NH2
1462	Ac-LDLKNYIDKQLLPVKNQSSUSISNIETVIEFQQKN-NH2
1463	Ac-DLKNYIDKQLLPVKNQSSUSISNIETVIEFQQKNN-NH2
5 1464	Ac-LKNYIDKQLLPVKNQSSUSISNIETVIEFQQKNNR-NH2
1465	Ac-KNYIDKQLLPVKNQSSUSISNIETVIEFQQKNRNL-NH2
1466	Ac-NYIDKQLLPVKNQSSUSISNIETVIEFQQKNRLL-NH2
1467	Ac-YIDKQLLPVKNQSSUSISNIETVIEFQQKNRLLLE-NH2
1468	Ac-IDKQLLPVKNQSSUSISNIETVIEFQQKNRLLLEI-NH2
1469	Ac-DKQLLPVKNQSSUSISNIETVIEFQQKNRLLLEIT-NH2
1470	Ac-KQLLPVKNQSSUSISNIETVIEFQQKNRLLLEITR-NH2
10 1471	Ac-QLLPVKNQSSUSISNIETVIEFQQKNRLLLEITRE-NH2
1472	Ac-VYPSDEYDASISQVNEEINQALA
1473	QVNEEINQALAYIRKADELLENV-NH2
1474	VYPSDEYDASISQVNEEINQALAYIRKADELLENV
1475	Ac-DEYDASISQVNEEINQALAYIREADEL-NH2
1476	Ac-DEYDASISQVNEKINQALAYIREADEL-NH2
1477	Ac-DDECLNSVKNGTYDFPKFEEESKLNREIKGVKLS-NH2
15 1478	Ac-DDE-Abu-LNSVKNGTYDFPKFEEESKLNREIKGVKLS-NH2
1479	Ac-YHKCDECLNSVKNGTYDFPKFEEESKLNREIKGVKLSS-NH2
1480	Ac-YHK-Abu-DDE-Abu-LNSVKNGTYDFPKFEEESKLNREIKGVKLSS-NH2
1481	Ac-YTSLIHSLIEESQIQQEKNEQELLELDKWASLWNWF-NH2
1482	Ac-YTSLIHSLIEESQNQQEKNEYELLELDKWASLWNWF-NH2
1483	Ac-YTSLIHSLIEESQIQQEKNEYELLELDKWASLWNWF-NH2
1484	Ac-YTSLIHSLIEESQIQQEKNEYELQKLDKWASLWNWF-NH2
20 1485	Ac-YTSLIHSLIEESQNQQEKNEQELQKLDKWASLWNWF-NH2
1486	Ac-YTSLIHSLIEESQNQQEKNEYELQKLDKWASLWNWF-NH2
1487	Ac-YTSLIHSLIEESQIQQEKNEQELQKLDKWASLWNWF-NH2
1488	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWETF-NH2
1489	Ac-YTSLIHSLIEESQIQQEKNEQELLELDKWASLWETF-NH2
1490	Ac-YTSLIHSLIEESQNQQEKNEYELLELDKWASLWETF-NH2
1491	Ac-YTSLIHSLIEESQIQQEKNEYELLELDKWASLWETF-NH2
25 1492	Ac-YTSLIHSLIEESQIQQEKNEYELQKLDKWASLWETF-NH2
1493	Ac-YTSLIHSLIEESQNQQEKNEQELQKLDKWASLWETF-NH2
1494	Ac-YTSLIHSLIEESQNQQEKNEYELQKLDKWASLWETF-NH2
1495	Ac-YTSLIHSLIEESQIQQEKNEQELQKLDKWASLWETF-NH2
1496	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKEWTF-NH2
1497	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIWASLWETF-NH2
1498	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAKWASLWETF-NH2
30 1499	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWASLWETF-NH2
1500	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIWAGLWETF-NH2
1501	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAKWAGLWETF-NH2
1502	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWAGLWETF-NH2

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No.	Sequence
1503	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLIWAGLWAWF-NH2
1504	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLAKWAGLWAWF-NH2
1505	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLIKWAGLWAWF-NH2
1506	Ac-WQEWQKITALLEQAQIQQEKGEYELQKLDKQEQF-NH2
5 1507	Ac-WQEWQKITALLEQAQIQQEKGEYELLELDKWEIF-NH2
1508	Ac-WQEWQKITALLEQAQIQQEKGEYELQKLAKWEIF-NH2
1509	Ac-WQEWQKITALLEQAQIQQEKGEYELQKLDWQWEIF-NH2
1510	Ac-WQEWQKITALLEQAQIQQEKGEYELLELAKWEIF-NH2
1511	Ac-WQEWQKITALLEQAQIQQEKNEYELLELDKWEIF-NH2
1512	Ac-WQEWQKITALLEQAQIQQEKNEYELLEELIEWASLWEIF-NH2
1513	Ac-WQEWQKITALLEQAQIQQEKNEYELLELIEWAGLWEIF-NH2
10 1514	Ac-WQEWQKITALLEQAQIQQEKNEYELLELIEWAGLWAWF-NH2
1515	Ac-WQEWREITALLEQAQIQQEKNEYELQKLIWASLWEIF-NH2
1516	Ac-WQEWREIQQEKNEYELQKLDKASLWEIF-NH2
1517	Ac-WQEWREIQQEKGEYELQKLIWEIF-NH2
1518	Ac-WQEWQAQIQQEKNEYELQKLDKASLWEIF-NH2
1519	Ac-WQEWQAQIQQEKGEYELQKLIWEIF-NH2
1520	PEG-GWQEWQRITALLEQAQIQQERNEYELQRLDEWASLWEIF-NH2
15 1521	Ac-GWQEWQRITALLEQAQIQQERNEYELQRLDEWASLWEIF-NH2
1522	PEG-YTSLITALLEQAQIQQERNEQELLELDWASLWEIF-NH2
1523	Ac-YTSLITALLEQAQIQQERNEQELLELDWASLWEIF-NH2
1526	PEG-GWQEWQRITALLEQAQIQQERNEYELQELDEWASLWEIF-NH2
1527	Ac-GWQEWQRITALLEQAQIQQERNEYELQELDEWASLWEIF-NH2
1528	PEG-YTSLIGSLIEESQIQQERNEQELLELDWASLWEIF-NH2
1529	PEG-GWQEWQRITALLEQAQIQQERNEYELQRLDRWASLWEIF-NH2
1530	Ac-GWQEWQRITALLEQAQIQQERNEYELQRLDRWASLWEIF-NH2
20 1531	PEG-GWQEWQRITALLEQAQIQQERNEYELQELDRWASLWEIF-NH2
1532	Ac-GWQEWQRITALLEQAQIQQERNEYELQELDRWASLWEIF-NH2
1533	PEG-YTSLIGSLIEESQIQQERNEQELLELDWASLWEIF-NH2
1534	Ac-YTSLIGSLIEESQIQQERNEQELLELDWASLWEIF-NH2
1538	Ac-YTSLIHSLEESQIQQEK-OH
1539	NEQELLELDK
1540	WASLWEIF-NH2
1542	Ac-AAWQKITALLEQAQIQQEKNEYELQKLDKASLWEIF-NH2
25 1543	Ac-WQEAALKITALLEQAQIQQEKNEYELQKLDKASLWEIF-NH2
1544	Ac-WQEWQAAAALEQAQIQQEKNEYELQKLDKASLWEIF-NH2
1545	Ac-WQEWQKITAAAEQAQIQQEKNEYELQKLDKASLWEIF-NH2
1546	Ac-WQEWQKITALLAAQAQIQQEKNEYELQKLDKASLWEIF-NH2
1547	Ac-WQEWQKITALLQAAAAQEKNEYELQKLDKASLWEIF-NH2
1548	Ac-WQEWQKITALLQAQIAAANEYELQKLDKASLWEIF-NH2
1549	Ac-WQEWQKITALLQAQIQQEKAAAEQKLDKASLWEIF-NH2
1550	Ac-WQEWQKITALLQAQIQQEKNEYAAAKLDKASLWEIF-NH2
1551	Ac-WQEWQKITALLQAQIQQEKNEYELQAAAKWASLWEIF-NH2
30 1552	Ac-WQEWQKITALLQAQIQQEKNEYELQKLDAAASLWEIF-NH
1553	Ac-WQEWQKITALLQAQIQQEKNEYELQKLDKAAAAEWF-NH
1554	Ac-WQEWQKITALLQAQIQQEKNEYELQKLDKASLWAAA-NH
1556	Ac-YTSLIHSLEESQIQQEKNEQELLELDKASLWEIF-NH2

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No.	Sequence
1557	Ac-YTSLIHSLIEESQNQEKNEQELLELDKWASLWNWF-NH2
1558	Ac-ERTLDFHDS-NH2
1559	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN (W) F-NH2
1563	Ac-YTSLIHSLIEESQN (Q) QEKNEQELLELDKWASLWNWF-NH2
5 1564	Ac-YTSLIHSLIEESQNQQDKWASLWNWF-NH2
1566	Ac-FYEIIMDIEQNNVQGGKGIQQLQKWEDWVGWIGNI-NH2
1567	Ac-INQTIWNHGNIITLGEWYNQTKDLQQKFYEIIMDIE-NH2
1568	Ac-WNHGNIITLGEWYNQTKDLQQKFYEIIMDIEQNNVQ-NH2
1572	Ac-YTSLIHSLIEESENQQEKNEQELLELDKWASLWNWF-NH2
1573	Ac-YTSLIHSLIEESQDQQEKNEQELLELDKWASLWNWF-NH2
1574	Ac-YTSLIHSLIEESQNEQEKNEQELLELDKWASLWNWF-NH2
1575	c-YTSLIHSLIEESQNQEEKNEQELLELDKWASLWNWF-NH2
1576	Ac-YTSLIHSLIEESQNQQEKDEQELLELDKWASLWNWF-NH2
10 1577	Ac-LGEWYNQTKDLQQKFYEIIMDIEQNNVQGGKGIQQLQK-NH2
1578	Ac-WYNQTKDLQQKFYEIIMDIEQNNVQGGKGIQQLQK-NH2
1579	Ac-YTSLIHSLIEESQNQQEKNEEELLELDKWASLWNWF-NH2
1580	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWDF-NH2
1586	Ac-XTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWX-NH2
1588	Ac-YNQTKDLQQKFYEIIMDIEQNNVQGGKGIQQLQK-NH2
1598	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF
1600	Ac-TLTQARQLLSGIVQQNNLLRAIEAQHLLQLTVWGIQQLQAR-NH2
15 1603	Ac-LQQKFYEIIMDIEQNNVQGGKGIQQLQKWEDWVGW-NH2
1627	Ac-YTSLIHSLIEESQNQQEKNEQELLALDKWASLWNWF-NH2
1628	Ac-YTSLIHSLIEESQNQQEKNEQELLEADKWASLWNWF-NH2
1629	Ac-YTSLIHSLIEESQNQQEKNEQELLELAKWASLWNWF-NH2
1630	Ac-YTSLIHSLIEESQNQQEKAEQELLELDKWASLWNWF-NH2
1631	Ac-YTSLIHSLIEESQNQQEKNAQELLELDKWASLWNWF-NH2
1632	Ac-YTSLIHSLIEESQNQQEKNEAEELLELDKWASLWNWF-NH2
1634	Ac-WQEWQKITALLEQAQIQQEKNEQELQKLDKWASLWEWF-NH2
20 1635	Ac-WQEWQKITALLEQAQIQQEKAEYELQKLDKWASLWEWF-NH2
1636	Ac-WQEWQKITALLEQAQIQQEKNAEYELQKLDKWASLWEWF-NH2
1637	Ac-WQEWQKITALLEQAQIQQEKNEAELEQKLDKWASLWEWF-NH2
1644	Ac-EYDLRRWEK-NH2
1645	Ac-EQELLELDK-NH2
1646	Ac-EYELQKLDK-NH2
1647	Ac-WQEWQKITALLEQAQIQQEKNEQELLKLDKWASLWEWF-NH2
1648	Ac-WQEWQKITALLEQAQIQQEKNEQELLELDKWASLWEWF-NH2
25 1649	Ac-WQEWQKITALLEQAQIQQEKNDKWASLWEWF-NH2
1650	Ac-YTSLIHSLIEESQNQAQEKNEQELLELDKWASLWNWF-NH2
1651	Ac-YTSLIHSLIEESQNQQAQEKNEQELLELDKWASLWNWF-NH2
1652	Ac-YTSLIHSLIEESQNQQAQEKNEQELLELDKWASLWNWF-NH2
1653	Ac-YTSLIHSLIEESANQQAQEKNEQELLELDKWASLWNWF-NH2
1654	Ac-YTSLIHSLIEESQAQQAQEKNEQELLELDKWASLWNWF-NH2
1655	Ac-YTSLIHSLIEESQNAQEKNEQELLELDKWASLWNWF-NH2
1656	Ac-YTSLIHSLIEESQNQQAQEKNEQELLELDKWASLWNWF-NH2
1657	Ac-YTSLIHSLIEESQNQQAQEKNEQELLELDKWASLWNWF-NH2
30 1658	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1659	Ac-YTSLIHSLAEESQNQQAQEKNEQELLELDKWASLWNWF-NH2
1660	Ac-YTSAIHSLIEESQNQQAQEKNEQELLELDKWASLWNWF-NH2
1661	Ac-YTSLAHSLIEESQNQQAQEKNEQELLELDKWASLWNWF-NH2

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No.	Sequence
1662	Ac-YTSLIASLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1663	Ac-ATSLIHSLEESQNQQEKNEQELLELDKWASLWNWF-NH2
1664	Ac-YASLIHSLEESQNQQEKNEQELLELDKWASLWNWF-NH2
1665	Ac-YTALIHSLEESQNQQEKNEQELLELDKWASLWNWF-NH2
5 1666	Ac-RIQDLEKYVEDTKIDLWSYNAELLVALENQ-NH2
1667	Ac-HTIDLTDSMNKLFKTRRQLREN-NH2
1668	Ac-SEMNKLFKTRRQLREN-NH2
1669	Ac-VFPSDEADASISQVNEKINQSLAFIRKSDELLHNV-NH2
1670	Ac-VFPSDEFAASISQVNEKINQSLAFIRKSDELLHNV-NH2
1671	Ac-VFPSDEFDASISAVNEKINQSLAFIRKSDELLHNV-NH2
1672	Ac-VFPSDEFDASISQANEKINQSLAFIRKSDELLHNV-NH2
1673	Ac-VFPSDEFDASISQVAEKINQSLAFIRKSDELLHNV-NH2
1674	Ac-WQEWQKITAALEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
10 1675	Ac-WQEWQKITALAEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1676	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1677	Ac-WQEWQKITALLEQAQAQQEKNEYELQKLDKWASLWEWF-NH2
1678	Ac-WQEWQKITALLEQAQIAQEKNEYELQKLDKWASLWEWF-NH2
1679	Ac-WQEWQKITALLEQAQIQAEKNEYELQKLDKWASLWEWF-NH2
1680	Ac-VFPSDEFDASISQVNEKINQSAAFIRKSDELLHNV-NH2
1681	Ac-VFPSDEFDASISQVNEKINQSLAAIRKSDELLHNV-NH2
1682	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
15 1683	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
1684	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLANV-NH2
1685	Ac-WQEWQKITALLEQAQIQQAKNEYELQKLDKWASLWEWF-NH2
1687	Ac-WQEWQKITALLEQAQIQQEKNEYELQALDKWASLWEWF-NH2
1688	Ac-WQEWQKITALLEQAQIQQEKNEYELQKADKWASLWEWF-NH2

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30

It is to be understood that the peptides listed in Table 2 and in the Example presented in Section 11, below, are also intended to fall within the scope of the present invention. As discussed above, those peptides depicted in Table 2 and in  
5 the Example presented, below, that do not already contain enhancer peptide sequences (that is, do not represent hybrid polypeptides) can be utilized in connection with the enhancer peptide sequences and teaching provided herein to generate hybrid polypeptides. Further, the core polypeptides and the  
10 core polypeptide of the hybrid polypeptides shown in Table 2, FIG. 13 and the Example presented in Section 11, below, can be used with any of the enhancer peptide sequences described herein to routinely produce additional hybrid polypeptides, which are also intended to fall within the scope of the present invention.

15 For example, peptide DP397, depicted in the Example presented in Section 11 represents a core polypeptide, and is intended to fall within the scope of the present invention. In addition, hybrid polypeptides comprising the DP397 core polypeptide plus one or more enhancer polypeptide sequences  
20 described herein are also intended to fall within the scope of the present invention.

It is noted that while a number of the polypeptides listed in Table 2 and FIG. 13 are depicted with modified, e.g., blocked amino and/or carboxy termini or d-isomeric amino acids (denoted by residues within parentheses), it is  
25 intended that any polypeptide comprising a primary amino acid sequence as depicted to Table 2 and FIG. 13 is also intended to be part of the present invention.

The core polypeptide sequences, per se, shown in Table 2, FIG. 13 and the Example presented, below, in Section 11 ,  
30 as well as the hybrid polypeptides comprising such core polypeptides, can exhibit antiviral, and/or anti-fusogenic activity and/or can exhibit an ability to modulate

intercellular processes that involve coiled-coil peptide structures. In addition, such peptides can also be utilized as part of screening methods for identifying compounds, including peptides, with such activities. Among the core polypeptide sequences are, for example, ones which have been derived from individual viral protein sequences. Also among the core polypeptide sequences are, for example, ones whose amino acid sequences are derived from greater than one viral protein sequence (e.g., an HIV-1, HIV-2 and SIV -derived core polypeptide).

10 In addition, such core polypeptides can exhibit amino acid substitutions, deletions and/or insertions as discussed, above, for enhancer polypeptide sequences. In instances wherein the core polypeptide exhibits antiviral and/or antifusogenic activity such modifications preferably do not  
15 abolish (either per se or as part of a hybrid polypeptide) this activity.

With respect to amino acid deletions, it is preferable that the resulting core polypeptide is at least about 4-6 amino acid residues in length. With respect to amino acid  
20 insertions, preferable insertions are no greater than about 50 amino acid residues, and, more preferably no more than about 15 amino acid residues. It is also preferable that core polypeptide insertions be amino- and/or carboxy-terminal insertions.

Among the amino acid substitutions, deletions, and/or  
25 insertions of the core or hybrid polypeptides of the invention are ones which correspond to amino acid substitutions, deletions and/or insertions found in mutants, e.g., naturally occurring mutants, of the endogenous protein sequence from which a particular core polypeptide is derived.

30 For example, if the core polypeptide is derived from a viral protein, and this core polypeptide (either per se or as part of a hybrid polypeptide) exhibits antiviral activity

against that or another virus, it is possible that variants (e.g., variant strains) of the virus may exist or may ultimately arise that exhibit some level of resistance to the peptide relative to the peptide's antiviral effect on the virus strain from which the original endogenous core polypeptide sequence was derived.

In order to generate core polypeptides that exhibit antiviral activity toward such resistant virus strains, modifications to the original core polypeptide can be introduced. In particular, isolates of the resistant virus can readily be isolated by one of skill in the art using standard techniques. Determination of the sequence within the resistant virus corresponding to the original core polypeptide can also routinely be determined and compared to the original core polypeptide.

In the event the corresponding sequence obtained from the mutant, resistant strain differs from the sequence of the core polypeptide, modifications to the core polypeptide can be introduced such that the resulting modified core polypeptide has the same sequence as the corresponding region in the resistant virus.

The resulting modified core polypeptide, either per se or as part of a hybrid polypeptide, will exhibit antiviral properties against the viral strain that had been resistant to the original core polypeptide. Such methods can be utilized, therefore, to identify core polypeptides that exhibit antiviral activity against virus strains that are or have become resistant to the antiviral activity of other core polypeptides.

One particular, but non-limiting example of the successful use of such a method to produce a modified core polypeptide that exhibits antiviral activity against a viral strain resistant to a "parent" core polypeptide is described in the Example presented, below, in Section 11.

In one embodiment, such modified core polypeptides that exhibit antiviral activity against strains resistant to the "parent" core polypeptide are ones in which amino acid substitutions, insertions and/or deletions have been introduced which modify the "parent" core polypeptide such that an N-glycosylation or O-glycosylation consensus sequence that was present in the "parent" core polypeptide has been abolished in the resulting modified core polypeptide.

For example, the consensus sequence for an N-glycosylation site is -N-X-S/T, where S/T is either serine or threonine and X is any amino acid except proline or aspartic acid. Thus, in one embodiment, a parent core polypeptide exhibiting such a consensus sequence can be modified via amino acid insertion, substitution and/or deletion such that this consensus sequence is abolished in the modified core polypeptide.

Among such amino and/or carboxy-terminal insertions are ones which comprise amino acid sequences amino and/or carboxy to the endogenous protein sequence from which the core polypeptide is derived. For example, if the core polypeptide is derived from gp41 protein, such an insertion would comprise an amino and/or carboxy-terminal insertion comprising a gp41 amino acid sequence adjacent to the gp41 core polypeptide sequence. Such amino and/or carboxy terminal insertions can typically range from about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 amino acid residues amino to and/or carboxy to the original core polypeptide.

The hybrid polypeptides of the invention can still further comprise additional modifications that readily allow for detection of the polypeptide. For example, the hybrid polypeptides can be labeled, either directly or indirectly. Peptide labeling techniques are well known to those of skill in the art and include, but are not limited to, radioactive, fluorescent and colorimetric techniques. Indirect labeling

techniques are also well known to those of skill in the art and include, but are not limited to, biotin/streptavidin labeling and indirect antibody labeling.

The invention further relates to the association of the  
5 enhancer polypeptide sequences to types of molecules other than peptides. For example, the enhancer peptide sequences may be linked to nucleic acid molecules (e.g., DNA or RNA) or any type of small organic molecule for the purpose of enhancing the pharmacokinetic properties of said molecules.

10

#### 5.2. SYNTHESIS OF PEPTIDES

The enhancer, core and hybrid polypeptides of the invention may be synthesized or prepared by techniques well known in the art. See, for example, Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman  
15 and Co., NY, which is incorporated herein by reference in its entirety. Hybrid polypeptides may be prepared using conventional step-wise solution or solid phase synthesis, fragment condensation, Fmoc or Boc chemistry. (see, e.g., Chemical Approaches to the Synthesis of Peptides and  
20 Proteins, Williams et al., Eds., 1997, CRC Press, Boca Raton Florida, and references cited therein; Solid Phase Peptide Synthesis: A Practical Approach, Atherton & Sheppard, Eds., 1989, IRL Press, Oxford, England, and references cited therein). Likewise the amino- and/or carboxy-terminal  
25 modifications.

In general, these methods can comprise the sequential addition of one or more amino acids or suitably protected amino acids to a growing peptide chain. Normally, either the amino or carboxyl group of the first amino acid is protected by a suitable protecting group. The protected or derivatized  
30 amino acid can then be either attached to an inert solid support or utilized in solution by adding the next amino acid in the sequence having the complementary (amino or carboxyl)

group suitably protected, under conditions suitable for forming the amide linkage. The protecting group is then removed from this newly added amino acid residue and the next amino acid (suitably protected) is then added, and so forth.

5 After all the desired amino acids have been linked in the proper sequence, remaining protecting groups and any solid support can be removed either sequentially or concurrently to afford the desired final polypeptide. By simple modification of this general procedure, it is possible to add more than one amino acid at a time to a growing chain, for example, by  
10 coupling (under condition that do not racemize chiral centers) a protected tripeptide with a properly protected dipeptide to form, after deprotection, a pentapeptide.

Typical protecting groups include T-butyloxycarbonyl (Boc), 9-fluorenylmethoxycarbonyl (Fmoc), benzyloxycarbonyl  
15 (Cbz), p-toluenesulfonyl (Tos); 2,4-dinitrophenyl, benzyl (Bzl), biphenylisopropoxy-carboxycarbonyl, cyclohexyl, isopropyl, acetyl, o-nitrophenylsulfonyl, and the like. Of these, Boc and Fmoc are preferred.

Typical solid supports are generally cross-linked  
20 polymeric materials. These include, but are not limited to, divinylbenzene cross-linked styrene-based polymers, for example, divinylbenzene-hydroxymethylstyrene copolymers, divinylbenzene-chloromethylstyrene copolymers, and divinylbenzene-benzhydrylaminopolystyrene copolymers. Such  
25 copolymers offer the advantage of directly introducing a terminal amide functional group into the peptide chain, which function is retained by the chain when the chain is cleaved from the support.

Polypeptides containing either L- or D-amino acids may be synthesized in this manner.

30 Polypeptide composition can be confirmed by quantitative amino acid analysis and the specific sequence of each peptide may be determined by sequence analysis.

The enhancer, core and hybrid polypeptides of the invention can be purified by art-known techniques such as normal and reverse phase high performance liquid chromatography, ion exchange chromatography, gel electrophoresis, affinity chromatography, size exclusion, precipitation and the like. The actual conditions used to purify a particular polypeptide will depend, in part, on synthesis strategy and on factors such as net charge, hydrophobicity, hydrophilicity, solubility, stability etc., and will be apparent to those having skill in the art.

Hybrid, enhancer and core polypeptides may also be made using recombinant DNA techniques. Here, the nucleotide sequences encoding the polypeptides of the invention may be synthesized, and/or cloned, and expressed according to techniques well known to those of ordinary skill in the art. See, for example, Sambrook, et al., 1989, Molecular Cloning, A Laboratory Manual, Vols. 1-3, Cold Spring Harbor Press, NY.

One may obtain the DNA segment encoding the polypeptide of interest using a variety of molecular biological techniques, generally known to those skilled in the art. For example, polymerase chain reaction (PCR) may be used to generate the DNA fragment encoding the protein of interest. Alternatively, the DNA fragment may be obtained from a commercial source.

The DNA encoding the polypeptides of interest may be recombinantly engineered into a variety of host vector systems that also provide for replication of the DNA in large scale. These vectors can be designed to contain the necessary elements for directing the transcription and/or translation of the DNA sequence encoding the hybrid polypeptide.

Vectors that may be used include, but are not limited to, those derived from recombinant bacteriophage DNA, plasmid DNA or cosmid DNA. For example, plasmid vectors such as

pcDNA3, pBR322, pUC 19/18, pUC 118, 119 and the M13 mp series of vectors may be used. Bacteriophage vectors may include  $\lambda$ gt10,  $\lambda$ gt11,  $\lambda$ gt18-23,  $\lambda$ ZAP/R and the EMBL series of bacteriophage vectors. Cosmid vectors that may be utilized  
5 include, but are not limited to, pJB8, pCV 103, pCV 107, pCV 108, pTM, pMCS, pNNL, pHSG274, COS202, COS203, pWE15, pWE16 and the charomid 9 series of vectors.

Alternatively, recombinant virus vectors including, but not limited to, those derived from viruses such as herpes virus, retroviruses, vaccinia viruses, adenoviruses, adeno-  
10 associated viruses or bovine papilloma viruses plant viruses, such as tobacco mosaic virus and baculovirus may be engineered.

In order to express a biologically active polypeptide, the nucleotide sequence coding for the protein may be  
15 inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for the transcription and translation of the inserted coding sequences. Methods which are well known to those skilled in the art can be used to construct expression vectors having  
20 the hybrid polypeptide coding sequence operatively associated with appropriate transcriptional/translational control signals. These methods include in vitro recombinant DNA techniques and synthetic techniques. See, for example, the techniques described in Sambrook, et al., 1992, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory,  
25 N.Y. and Ausubel et al., 1989, Current Protocols in Molecular Biology, Greene Publishing Associates & Wiley Interscience, N.Y., each of which are incorporated herein by reference in its entirety.

The nucleic acid molecule encoding the hybrid, enhancer  
30 and core polypeptides of interest may be operatively associated with a variety of different promoter/enhancer elements. The promoter/enhancer elements may be selected to

optimize for the expression of therapeutic amounts of protein. The expression elements of these vectors may vary in their strength and specificities. Depending on the host/vector system utilized, any one of a number of suitable transcription and translation elements may be used. The promoter may be in the form of the promoter which is naturally associated with the gene of interest.

Alternatively, the DNA may be positioned under the control of a recombinant or heterologous promoter, i.e., a promoter that is not normally associated with that gene. For example, tissue specific promoter/enhancer elements may be used to regulate the expression of the transferred DNA in specific cell types.

Examples of transcriptional control regions that exhibit tissue specificity which have been described and could be used include, but are not limited to, elastase I gene control region which is active in pancreatic acinar cells (Swift et al., 1984, Cell 38:639-646; Ornitz et al., 1986, Cold Spring Harbor Symp. Quant. Biol. 50:399-409; MacDonald, 1987, Hepatology 7:42S-51S); insulin gene control region which is active in pancreatic beta cells (Hanahan, 1985, Nature 315:115-122); immunoglobulin gene control region which is active in lymphoid cells (Grosschedl et al., 1984, Cell 38:647-658; Adams et al., 1985, Nature 318:533-538; Alexander et al., 1987, Mol. Cell. Biol. 7:1436-1444); albumin gene control region which is active in liver (Pinkert et al., 1987, Genes and Devel. 1:268-276); alpha-fetoprotein gene control region which is active in liver (Krumlauf et al., 1985, Mol. Cell. Biol. 5:1639-1648; Hammer et al., 1987, Science 235:53-58); alpha-1-antitrypsin gene control region which is active in liver (Kelsey et al., 1987, Genes and Devel. 1:161-171); beta-globin gene control region which is active in myeloid cells (Magram et al., 1985, Nature 315:338-340; Kollias et al., 1986, Cell 46:89-94); myelin basic

protein gene control region which is active in oligodendrocyte cells in the brain (Readhead et al., 1987, Cell 48:703-712); myosin light chain-2 gene control region which is active in skeletal muscle (Shani, 1985, Nature 314:283-286); and gonadotropic releasing hormone gene control region which is active in the hypothalamus (Mason et al., 1986, Science 234:1372-1378). Promoters isolated from the genome of viruses that grow in mammalian cells, (e.g., vaccinia virus 7.5K, SV40, HSV, adenoviruses MLP, MMTV, LTR and CMV promoters) may be used, as well as promoters produced by recombinant DNA or synthetic techniques.

In some instances, the promoter elements may be constitutive or inducible promoters and can be used under the appropriate conditions to direct high level or regulated expression of the nucleotide sequence of interest.

15 Expression of genes under the control of constitutive promoters does not require the presence of a specific substrate to induce gene expression and will occur under all conditions of cell growth. In contrast, expression of genes controlled by inducible promoters is responsive to the presence or absence of an inducing agent.

Specific initiation signals are also required for sufficient translation of inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where the entire coding sequence, including the initiation codon and adjacent sequences are inserted into the appropriate expression vectors, no additional translational control signals may be needed.

25 However, in cases where only a portion of the coding sequence is inserted, exogenous translational control signals, including the ATG initiation codon must be provided.

30 Furthermore, the initiation codon must be in phase with the reading frame of the protein coding sequences to ensure translation of the entire insert. These exogenous

translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of transcription attenuation sequences, enhancer elements, etc.

5

5.3. USES OF THE ENHANCER PEPTIDE SEQUENCES, CORE POLYPEPTIDES AND HYBRID POLYPEPTIDES OF THE INVENTION

As discussed above, the enhancer peptide sequences of the invention can be utilized to enhance the pharmacokinetic properties of any core polypeptide through linkage of the  
10 core polypeptide to the enhancer peptide sequences to form hybrid polypeptides. The observed enhancement of pharmacokinetic properties is relative to the pharmacokinetic properties of the core polypeptide alone. Standard  
15 pharmacokinetic character parameters and methods for determining and characterizing the pharmacokinetic properties of an agent such as a polypeptide are well known to those of skill in the art. Non-limiting examples of such methods are presented in the Examples provided below.

20 The enhancer peptide sequences of the invention can, additionally, be utilized to increase the in vitro or ex-vivo half-life of a core polypeptide to which enhancer peptide sequences have been attached. For example, enhancer peptide sequences can increase the half life of attached core polypeptides when the resulting hybrid polypeptides are  
25 present in cell culture, tissue culture or patient samples, (e.g., cell samples, tissue samples biopsies, or other sample containing bodily fluids).

The core polypeptides and hybrid polypeptides of the invention can also be utilized as part of methods for  
30 modulating (e.g., decreasing, inhibiting, disrupting, stabilizing or enhancing) fusogenic events. Preferably, such peptides exhibit antifusogenic or antiviral activity. The

peptides of the invention can also exhibit the ability to modulate intracellular processes involving coiled-coil peptide interactions.

In particular embodiments, the hybrid polypeptides and  
5 core polypeptides of the invention that exhibit antiviral activity can be used as part of methods for decreasing viral infection. Such antiviral methods can be utilized against, for example, human retroviruses, particularly HIV (human immunodeficiency virus), e.g., HIV-1 and HIV-2, and the human  
10 T-lymphocyte viruses (HTLV-I and HTLV-II), and non-human retroviruses, such as bovine leukosis virus, feline sarcoma and leukemia viruses, simian immunodeficiency viruses (SIV), sarcoma and leukemia viruses, and sheep progress pneumonia viruses.

The antiviral methods of the invention can also be  
15 utilized against non-retroviral viruses, including, but not limited to, respiratory syncytial virus (RSV), canine distemper virus, newcastle disease virus, human parainfluenza virus, influenza viruses, measles viruses, Epstein-Barr viruses, hepatitis B viruses and Mason-Pfizer viruses.

20 The above-recited viruses are enveloped viruses. The antiviral methods of the invention can also be utilized against non-enveloped viruses, including but not limited to picornaviruses such as polio viruses, hepatitis A virus, enterovirus, echoviruses, and coxsackie viruses, papovaviruses such as papilloma virus, parvoviruses,  
25 adenoviruses and reoviruses.

Other antifusogenic activities that can be modulated via methods that utilize the peptides of the invention include, but are not limited to modulation of neurotransmitter exchange via cell fusion, and sperm-egg fusion. Among the  
30 intracellular disorders involving coiled-coil interactions that can be ameliorated via methods that utilize the peptides

of the invention are disorder involving, for example, bacterial toxins.

The antifusion or antiviral activity of a given core polypeptide or hybrid polypeptide can routinely be  
5 ascertained via standard in vitro, ex vivo and animal model assays that, with respect to antiviral activity, can be specific or partially specific for the virus of interest and are well known to those of skill in the art.

The above description relates mainly to antiviral and antifusion-related activities of core and hybrid polypeptides  
10 of the invention. The hybrid polypeptides of the invention can also be utilized as part of any method for which administration or use of the core polypeptide alone might be contemplated. Use of hybrid polypeptides as part of such methods is particularly preferable in instances wherein an  
15 increase in the pharmacokinetic properties of the core polypeptide is desired. For example, insulin is utilized as part of treatment for certain types of diabetes. A hybrid polypeptide comprising an insulin or insulin fragment as the core polypeptide can, therefore, also be utilized as part of  
20 methods for ameliorating symptoms of forms of diabetes for which insulin is used and/or contemplated.

In addition to the above therapeutic methods, the peptides of the invention can still further be utilized as part of prognostic methods for preventing disorders,  
25 including, but not limited to disorders involving fusion events, intracellular processes involving coiled-coil peptides and viral infection that involves cell-cell and/or virus-cell fusion. For example, the core and hybrid polypeptides of the invention can be utilized as part of prophylactic methods of preventing viral infection.

30 The hybrid polypeptides of the invention can still further be utilized as part of diagnostic methods. Such methods can be either in vivo or in vitro methods. Any

diagnostic method that a particular core polypeptide can be utilized can also be performed using a hybrid polypeptide comprising the core polypeptide and a modification or primary amino acid sequence that allows detection of the hybrid polypeptide. Such techniques can reflect an improvement over diagnostic methods in that the increased half life of the hybrid polypeptide relative to the core polypeptide alone can increase the sensitivity of the diagnostic procedure in which it is utilized. Such diagnostic techniques include, but are not limited to imaging methods, e.g., in vivo imaging methods. In a non-limiting example of an imaging method, a structure that binds the core polypeptide of a hybrid polypeptide can be detected via binding to the hybrid polypeptide and imaging (either directly or indirectly) the bound hybrid polypeptide.

#### 5.4. PHARMACEUTICAL FORMULATIONS, DOSAGES AND MODES OF ADMINISTRATION

The peptides of the invention may be administered using techniques well known to those in the art. Preferably, agents are formulated and administered systemically. Techniques for formulation and administration may be found in "Remington's Pharmaceutical Sciences", latest edition, Mack Publishing Co., Easton, PA. Suitable routes may include oral, rectal, vaginal, lung (e.g., by inhalation), transdermal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few. For intravenous injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer to name a

few. In addition, infusion pumps may be used to deliver the peptides of the invention. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known  
5 in the art.

In instances wherein intracellular administration of the peptides of the invention or other inhibitory agents is preferred, techniques well known to those of ordinary skill in the art may be utilized. For example, such agents may be encapsulated into liposomes, or microspheres then  
10 administered as described above. Liposomes are spherical lipid bilayers with aqueous interiors. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external  
15 microenvironment and, because liposomes fuse with cell membranes, are effectively delivered into the cell cytoplasm. Additionally, due to their hydrophobicity, when small molecules are to be administered, direct intracellular administration may be achieved.

20 Nucleotide sequences encoding the peptides of the invention which are to be intracellularly administered may be expressed in cells of interest, using techniques well known to those of skill in the art. For example, expression vectors derived from viruses such as retroviruses, vaccinia viruses, adeno-associated viruses, herpes viruses, or bovine  
25 papilloma viruses, may be used for delivery and expression of such nucleotide sequences into the targeted cell population. Methods for the construction of such vectors and expression constructs are well known. See, for example, Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold  
30 Spring Harbor Press, Cold Spring Harbor NY, and Ausubel et al., 1989, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY.

Effective dosages of the peptides of the invention to be administered may be determined through procedures well known to those in the art which address such parameters as biological half-life, bioavailability, and toxicity. In particularly preferred embodiments, an effective hybrid polypeptide dosage range is determined by one skilled in the art using data from routine *in vitro* and *in vivo* studies well known to those skilled in the art. For example, *in vitro* cell culture assays of antiviral activity, such as the exemplary assays described in Section 7, below, for T1249, will provide data from which one skilled in the art may readily determine the mean inhibitory concentration (IC) of the peptide of the polypeptide necessary to block some amount of viral infectivity (e.g., 50%, IC<sub>50</sub>; or 90%, IC<sub>90</sub>). Appropriate doses can then be selected by one skilled in the art using pharmacokinetic data from one or more routine animal models, such as the exemplary pharmacokinetic data described in Section 10, below, for T1249, so that a minimum plasma concentration (C<sub>min</sub>) of the peptide is obtained which is equal to or exceeds the determined IC value.

Exemplary polypeptide dosages may be as low as 0.1 µg/kg body weight and as high as 10 mg/kg body weight. More preferably an effective dosage range is from 0.1 - 100 µg/kg body weight. Other exemplary dosages for peptides of the invention include 1-5 mg, 1-10 mg, 1-30 mg, 1-50 mg, 1-75 mg, 1-100 mg, 1-125 mg, 1-150 mg, 1-200 mg, or 1-250 mg of peptide. A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the

population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio  $LD_{50}/ED_{50}$ . Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the  $ED_{50}$  with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the  $IC_{50}$  (e.g., the concentration of the test compound which achieves a half-maximal inhibition of the fusogenic event, such as a half-maximal inhibition of viral infection relative to the amount of the event in the absence of the test compound) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography (HPLC) or any biological or immunological assay capable of measuring peptide levels.

The hybrid polypeptides of the invention can be administered in a single administration, intermittently, periodically, or continuously. For example, the polypeptides of the invention can be administered in a single administration, such as a single subcutaneous, a single intravenous infusion or a single ingestion. The polypeptides of the invention can also be administered in a plurality of intermittent administrations, including periodic administrations. For example, in certain embodiments the polypeptides of the invention can be administered once a

week, once a day, twice a day (e.g., every 12 hours), every six hours, every four hours, every two hours, or every hour. The polypeptides of the invention may also be administered continuously, such as by a continuous subcutaneous or  
5 intravenous infusion pump or by means of a subcutaneous or other implant which allows the polypeptides to be continuously absorbed by the patient.

The hybrid polypeptides of the invention can also be administered in combination with at least one other therapeutic agent. Although not preferred for HIV therapy,  
10 administration for other types of therapy (e.g., cancer therapy) can be performed concomitantly or sequentially, including cycling therapy (that is, administration of a first compound for a period of time, followed by administration of a second antiviral compound for a period of time and  
15 repeating this sequential administration in order to reduce the development of resistance to one of the therapies).

In the case of viral, e.g., retroviral, infections, an effective amount of a hybrid polypeptide or a pharmaceutically acceptable derivative thereof can be  
20 administered in combination with at least one, preferably at least two, other antiviral agents.

Taking HIV infection as an example, such antiviral agents can include, but are not limited to DP-107 (T21), DP-178 (T20), any other core polypeptide depicted in Table 2 derived from HIV-1 or HIV-2, any other hybrid polypeptide  
25 whose core polypeptide is, at least in part, derived from HIV-1 or HIV-2, cytokines, e.g., rIFN  $\alpha$ , rIFN  $\beta$ , rIFN  $\gamma$ ; inhibitors of reverse transcriptase, including nucleoside and non-nucleoside inhibitors, e.g., AZT, 3TC, D4T, ddI, adefovir, abacavir and other dideoxynucleosides or  
30 dideoxyfluoronucleosides, or delaviridine mesylate, nevirapine, efavirenz; inhibitors of viral mRNA capping, such as ribavirin; inhibitors of HIV protease, such as ritonavir,

nelfinavir mesylate, amprenavir, saquinavir, saquinavir mesylate, indinavir or ABT378, ABT538 or MK639; amphotericin B as a lipid-binding molecule with anti-HIV activity; and castanospermine as an inhibitor of glycoprotein processing.

5       The hybrid and/or core polypeptides of the invention may, further, be utilized prophylactically for the prevention of disease. Hybrid and/or core polypeptides can act directly to prevent disease or, alternatively, can be used as vaccines, wherein the host raises antibodies against the hybrid polypeptides of the invention, which then serve to  
10       neutralize pathogenic organisms including, for example, inhibiting viral, bacterial and parasitic infection.

For all such treatments described above, the exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's  
15       condition. (See e.g. Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1).

It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity, or to organ dysfunctions.  
20       Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the oncogenic disorder of interest will vary with the severity of the condition to be treated and the route of administration. The  
25       dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

Use of pharmaceutically acceptable carriers to formulate  
30       the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of

carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by subcutaneous injection, intravenous injection, by  
5 subcutaneous infusion or intravenous infusion, for example by pump. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries,  
10 suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve  
15 its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to the active ingredients, these  
20 pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees,  
25 capsules, or solutions. For oral administration of peptides, techniques such of those utilized by, e.g., Emisphere Technologies well known to those of skill in the art and can routinely be used.

The pharmaceutical compositions of the present invention  
30 may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating,

dragee-making, levigating, spray drying, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, emulsions and suspensions of the active compounds may be prepared as appropriate oily injection mixtures. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, liposomes or other substances known in the art for making lipid or lipophilic emulsions. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, trehalose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl

pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound  
5 doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the  
10 active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or  
15 liquid polyethylene glycols. In addition, stabilizers may be added.

In instances where an enhancement of the host immune response is desired, the hybrid polypeptides may be formulated with a suitable adjuvant in order to enhance the  
20 immunological response. Such adjuvants may include, but are not limited to mineral gels such as aluminum hydroxide; surface active substances such as lysolecithin, pluronic polyols, polyanions; other peptides; oil emulsions; and potentially useful adjuvants such as BCG and Corynebacterium  
25 parvum. Many methods may be used to introduce the vaccine formulations described here. These methods include but are not limited to oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, and intranasal routes.

30

6. EXAMPLE: IDENTIFICATION OF CONSENSUS AMINO  
ACID SEQUENCES THAT COMPRISE  
ENHANCER PEPTIDE SEQUENCES

The retroviral gp41 protein contains structural domains referred to as the  $\alpha$ -helix region located in the C-terminal region of the protein and the leucine zipper region located in the N-terminal region of the protein. Alignment of the enhancer peptide sequence regions contained within gp41 (FIG. 2A and 2B) of gp41 from all currently published isolate sequences of HIV-1, HIV-2 and SIV identified the consensus amino acid sequences shown in FIG. 1.

As described in detail in the Examples presented below, such sequences represent enhancer peptide sequences in that linkage of these peptide sequences to a variety of different core polypeptides enhances the pharmacokinetic properties of the resultant hybrid polypeptides.

7. EXAMPLE: HYBRID POLYPEPTIDES THAT FUNCTION  
AS POTENT INHIBITORS OF HIV-1 INFECTION

T1249, as depicted in FIG. 13, is a hybrid polypeptide comprising enhancer peptide sequences linked to an HIV core polypeptide. As demonstrated below, the T1249 hybrid polypeptide exhibits enhanced pharmacokinetic properties and potent *in vitro* activity against HIV-1, HIV-2, and SIV isolates, with enhanced activity against HIV-1 clinical isolates in HuPBMC infectivity assays *in vitro* as well as in the HuPBMC SCID mouse model of HIV-1 infection *in vivo*. In the biological assays described below, the activity of the T1249 is compared to the potent anti-viral T20 polypeptide. The T20 polypeptide, also known as DP-178, is derived from HIV-1 gp41 protein sequence, and is disclosed and claimed in U.S. patent No. 5,464,933.

## 7.1. MATERIALS AND METHODS

### 7.1.1. PEPTIDE SYNTHESIS AND PURIFICATION

Peptides were synthesized using Fast Moc chemistry. Generally, unless otherwise noted, the peptides contained  
5 amidated carboxyl termini and acetylated amino termini. Purification was carried out by reverse phase HPLC.

T1249 (Ac-WQEWKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH<sub>2</sub>) is a 39 amino acid peptide (MW = 5036.7) composed entirely of naturally occurring amino acids and is blocked at the amino terminus by an acetyl group and the carboxyl terminus is  
10 blocked by an amido group to enhance stability. T1387 is a 23 amino acid peptide lacking enhancer peptide sequences (Ac-TALLEQAQIQQEKNEYELQKLDK-NH<sub>2</sub>). Thus, T1387 represents the core polypeptide of the T1249 hybrid polypeptide. T1387 is blocked at its amino- and carboxy- termini in the same manner  
15 as T1249.

In particular, T1249 was synthesized using standard solid-phase synthesis techniques. The identity of the principal peak in the HPLC trace was confirmed by mass spectroscopy to be T1249.

20 T1249 was readily purified by reverse phase chromatography on a 6-inch column packed with a C18, 10 micron, 120A support.

### 7.1.2. VIRUS

The HIV-1<sub>LAI</sub> virus (Popovic, M. et al., 1984, Science  
25 224:497-508) was propagated in CEM cells cultured in RPMI 1640 containing 10% fetal calf serum. Supernatant from the infected CEM cells was passed through a 0.2µm filter and the infectious titer estimated in a microinfectivity assay using the AA5 cell line to support virus replication. For this  
30 purpose, 20µl of serially diluted virus was added to 20µl CEM cells at a concentration of 6 x 10<sup>5</sup>/ml in a 96-well microtitre plate. Each virus dilution was tested in triplicate. Cells

were cultured for seven days by addition of fresh medium every other day. On day 7 post infection, supernatant samples were tested for virus replication as evidenced by reverse transcriptase activity released to the supernatant.

5 The TCID<sub>50</sub> was calculated according to the Reed and Muench formula (Reed, L.J. et al., 1938, Am. J. Hyg. 27:493-497).

#### 7.1.3. CELL FUSION ASSAY

Approximately  $7 \times 10^4$  Molt-4 cells were incubated with  $1 \times 10^4$  CEM cells chronically infected with the HIV-1<sub>LAI</sub> virus in

10 96-well tissue culture plates in a final volume of 100  $\mu$ l culture medium (RPMI 1640 containing 10% heat inactivated FBS, supplemented with 1% L-glutamine and 1% Pen-Strep) as previously described (Matthews, T.J. et al., 1987, Proc. Natl. Acad. Sci. USA 84: 5424-5428). Peptide inhibitors were

15 added in a volume of 10  $\mu$ l and the cell mixtures were incubated for 24 hr. at 37°C in 5% CO<sub>2</sub>. At that time, multinucleated giant cells (syncytia, five cell widths or larger) were counted by microscopic examination at 10x and 40x magnification which allowed visualization of the entire

20 well in a single field. Treated cells were compared to infected, untreated controls and results expressed as percent inhibition of infected controls.

#### 7.1.4. MAGI-CCR-5 INFECTIVITY ASSAYS

Approximately  $1 \times 10^6$  Magi-CCR-5 cells (obtained through

25 the NIH AIDS Research and Reference Reagent Program, Division of AIDS, NIAID; Chackerian, B. et al., 1997, J. Virol. 71: 3932-3939) were seeded into a 48-well tissue culture plate (approximately  $2 \times 10^4$  cells/well in a volume of 300  $\mu$ l/well selective growth medium consisting of DMEM supplemented with

30 10% heat inactivated FBS, 1% L-glutamine, 1% Pen/Strep, Hygromycin B, Geneticin, and Puromycin) and allowed to attach overnight at 37°C, 5% CO<sub>2</sub>. Cell confluency was approximately

30% by the following day. Seeding medium was removed and diluted peptide inhibitor added in volumes of 50  $\mu$ l/well (media only in untreated controls), followed by 100  $\mu$ l/well of diluted virus (desired input virus titre of 100 - 200 pfu/well). Finally, 250  $\mu$ l of selective growth medium was added to each well and the plate incubated for 2 days at 37°C, 5% CO<sub>2</sub>. Fixing and staining were done according to the protocol provided by NIAID with the MAGI-CCR5 cells. Briefly, medium was removed from the plate and 500  $\mu$ l of fixative added to each well. Plates were allowed to fix for 5 minutes at room temp. Fixative was removed, each well washed twice with DPBS, and 200  $\mu$ l of staining solution added to each well. The plate was then incubated at 37°C, 5% CO<sub>2</sub>, for 50 minutes, staining solution removed, and each well washed twice with DPBS. The plate was allowed to air dry before blue cells were counted by microscopic, enumerating the entire well. Treated wells were compared to infected, untreated controls and results expressed as percent inhibition of infected controls.

#### 20 7.1.5. REVERSE TRANSCRIPTASE ASSAY

The micro-reverse transcriptase (RT) assay was adapted from Goff et al. (Goff, S. et al., 1981, J. Virol. 38: 239-248) and Willey et al. (Willey, R. et al., 1988, J. Virol. 62: 139-147). Supernatants from virus/cell cultures were adjusted to 1% Triton-X100. 10  $\mu$ l of each supernatant/Triton X-100 sample were added to 50  $\mu$ l of RT cocktail (75 mM KCl, 2 mM Cleavelands reagent, 5 mM MgCl<sub>2</sub>, 5  $\mu$ g/ml poly A, 0.25 units/ml oligo dT, 0.05% NP40, 50 mM Tris-HCl, pH 7.8, 0.5  $\mu$ M non-radioactive dTTP, and 10 cCi/ml <sup>32</sup>P-dTTP) in a 96-well U-bottom microtitre plate and incubated at 37°C for 90 min. After incubation, 40  $\mu$ l of reaction mixture from each well was transferred to a Schleicher and Schuell (S+S) dot blot apparatus, under partial vacuum, containing a gridded 96-well

filter-mat (Wallac catalog #1450-423) and filter backing saturated with 2x SSC buffer (0.3M NaCl and 0.003M sodium citrate). Each well was washed 4 times with at least 200  $\mu$ l 2x SSC using full vacuum. Minifold was disassembled and  
5 gridded filter paper removed and washed 3 times with 2x SSC. Finally, the filter membrane was drained on absorbent paper, allowed to air dry, and sealed in heat sealable bags. Samples were placed in a phosphorscreen cassette and an erased (at least 8 min) phosphorscreen applied and closed. Exposure was for 16 hr. Pixel Index Values (PIV), generated  
10 in volume reporting format retrieved from phosphorimaging (Molecular Dynamics Phosphorimager) blots, were used to determine the affected or inhibited fraction (Fa) for all doses of inhibitor(s) when compared to untreated, infected controls (analyzed by ImageQuant volume report, corrected for  
15 background).

#### 7.1.6. HUMAN PBMC INFECTIVITY/NEUTRALIZATION ASSAY

The prototypic assay used cell lines where the primary isolate assay utilizes PBMC, obtained through Interstate  
20 Blood Bank, activated for 2-3 days with a combination of OKT3 (0.5  $\mu$ g/ml) and CD28 antibodies (0.1  $\mu$ g/ml). The target cells were banded on lymphocyte separation medium (LSM), washed, and frozen. Cells were thawed as required and activated as indicated above a minimum of 2-3 days prior to  
25 assay. In this 96-well format assay, cells were at a concentration of  $2 \times 10^6$ /ml in 5% IL-2 medium and a final volume of 100  $\mu$ l. Peptide stock solutions were made in DPBS (1 mg/ml). Peptide dilutions were performed in 20% FBS RPMI 1640/5% IL-2 complete medium.

30

7.1.7. IN VIVO HU-PBMC SCID MODEL  
OF HIV-1 INFECTION

Female SCID mice (5-7 weeks old) received  $5-10 \times 10^7$  adult human PBMC injected intraperitoneally. Two weeks after  
5 reconstitution, mice were infected IP on day 0 with  $10^3$  TCID<sub>50</sub> HIV-1 9320 (AZT-sensitive isolate A018). Treatment with peptides was IP, bid, beginning day -1 and continuing through day 6. The extent of infection in blood cells, splenocytes, lymph nodes, and peritoneal cells was assayed by quantitative  
10 co-culture with human PBMC blasts weekly for three consecutive weeks following animal exsanguinations and tissue harvest (day 7, approximately 12-18 hours following the last drug treatment). Co-culture supernatants were evaluated for HIV-1 p24 antigen production as a measure of virus infection  
15 (Immunotek Coulter kits and protocol).

7.1.8. RAT PHARMACOKINETIC STUDIES

250-300 g male CD rats, double jugular catheter, obtained from Charles River Laboratories were used. Peptides were injected in one jugular catheter in a volume of 200  $\mu$ l  
20 of peptide solution (approximately 3.75 mg/ml), dosing solution concentration was determined using the Edelhoch method, (Edelhoch, 1967, Biochemistry 6:1948-1954) method and adjusted based on animal weight such that each animal received a dose of 2.5 mg/kg). Approximately 250-300  $\mu$ l of  
25 blood was removed at predetermined time intervals (0, 15, 30 min and 1, 2, 4, 6, and 8 hours) and added to EDTA capiject tubes. Plasma was removed from pelleted cells upon centrifugation and either frozen or immediately processed for fluorescence HPLC analysis.

30

#### 7.1.9. FLUORESCENCE HPLC ANALYSIS OF PLASMA SAMPLES

100  $\mu$ l of sample plasma was added to 900  $\mu$ l of precipitation buffer (acetonitrile, 1.0% TFA, detergent) resulting in precipitation of the majority of plasma  
5 proteins. Following centrifugation at 10,000 rpm for 10 min, 400  $\mu$ l of the supernatant was removed and added to 600  $\mu$ l of HPLC grade water. Serial dilutions were performed as dictated by concentration of peptide present in each sample in dilution buffer comprised of 40% precipitation buffer and  
10 60% HPLC water. In addition to sample dilutions, serial dilutions of dosing solution were performed in buffer as well as in plasma and used to generate a standard curve relating peak area to known concentration of peptide. This curve was then used to calculate concentration of peptide in plasma  
15 taking into account all dilutions performed and quantity injected onto column.

#### 7.1.10. XTT PROTOCOL

In order to measure cytotoxic/cytostatic effects of peptides, XTT assays (Weislow, O.S. et al., 1989, J. Natl.  
20 Cancer Inst. 81:577-586) were performed in the presence of varying concentrations of peptide in order to effectively establish a selective index (SI). A  $TC_{50}$  was determined in this assay by incubating cells in the presence and absence of serially diluted peptide followed by the addition of XTT. In  
25 surviving/metabolizing cells XTT is reduced to a soluble brown dye, XTT-formazan. Absorbance is read and comparisons made between readings in the presence and absence of peptide to determine a  $TC_{50}$  utilizing the Karber method (see. e.g., Lennette, E.H. et al., eds., 1969, "Diagnostic Procedures for  
30 Viral and Rickettsial Infections," American Public Health Association, Inc., fourth ed., pp. 47-52). Molt 4, CEM (80,000 cells/well) and a combination of the two cell types

(70,000 and 10,000 respectively) were plated and incubated with serially diluted peptide for 24 hours in a total volume of 100  $\mu$ l. Following incubation, 25  $\mu$ l of XTT working stock (1 mg/ml XTT, 250  $\mu$ M PMS in complete medium containing 5% DMSO) was added to each well and the plates incubated at 37°C. Color development was read and results used to express values generated from peptide containing wells as a percentage of the untreated control wells.

## 7.2. RESULTS

### 7.2.1. ANTIVIRAL ACTIVITY - FUSION ASSAYS

T1249 was directly compared to T20 in virus mediated cell-cell fusion assays conducted using chronically infected CEM cells mixed with uninfected Molt-4 cells, as shown in Table 3, below. T1249 fusion inhibition against lab isolates such as IIIB, MN, and RF is comparable to T20, and displays an approximately 2.5-5-fold improvement over T20. T1249 was also more active (3-28 fold improvement) than T20 against several syncytia-inducing clinical isolates, including an AZT resistant isolate (G691-2), a pre-AZT treatment isolate (G762-3), and 9320 (isolate used in HuPBMC-SCID studies). Most notably, T1249 was over 800-fold more potent than T20 against HIV-2 NIHZ.

TABLE 3

Virus Isolate	T20 (ng/ml)	n	T1249 (ng/ml)	n	Fold Difference
HIV-1 IIIB	2.5	9	1.0	9	2.5
HIV-1 G691-2 (AZT-R)	406.0	1	16.0	1	25
HIV-1 G762-3 (Pre-AZT)	340.1	1	12.2	1	28
HIV-1 MN	20.0	7	3.1	7	6

5	Virus Isolate	T20 (ng/ml)	n	T1249 (ng/ml )	n	Fold Differe nce
	HIV-1 RF	6.1	7	2.1	7	3
	HIV-1 9320	118.4	1	34.5	1	3
	HIV-2 NIHZ	3610.0	>10	4.3	2	840

#### 7.2.2. ANTIVIRAL ACTIVITY - Magi-CCR-5 INFECTIVITY ASSAYS

10        Magi-CCR-5 infectivity assays allow direct comparisons  
to be made of syncytia and non-syncytia inducing virus  
isolates, as well as comparisons between laboratory and  
clinical isolates. The assay is also a direct measure of  
virus infection (TAT expression following infection,  
transactivating an LTR driven beta-galactosidase production),  
15 as opposed to commonly used indirect measures of infectivity  
such as p24 antigen or reverse transcriptase production.  
Magi-CCR-5 infectivity assays (see Table 4 below) reveal that  
T1249 is consistently more effective than T20 against all  
isolates tested, in terms of both  $EC_{50}$  and  $V_n/V_o = 0.1$   
20 inhibition calculations. T1249 shows considerable  
improvement in potency against the clinical isolate HIV-1  
301714 (>25-fold), which is one of the least sensitive  
isolates to T20. In addition, T1249 is at least 100-fold  
more potent than T20 against the SIV isolate B670. These  
25 data, along with fusion data suggest that T1249 is a potent  
peptide inhibitor of HIV-1, HIV-2, and SIV.

TABLE 4

		T20		T1249			
5	Virus Isolate	EC-50	Vn/Vo=0.1	E C-50	Vn/Vo=0.1	EC-50 Fold Difference	Vn/Vo=0.1 Fold Difference
10	HIV-1 IIIB	42	80	8	10	5	8
	HIV-1 9320	11	50	1	6	11	8
	HIV-1 301714 (subtype B, NSI)	1065	4000	43	105	25	38
	HIV-1 G691-2 (AZT-R)	13	200	0.3	20	43	10
	HIV-1 pNL4-3	166	210	1	13	166	16
15							
	SIV-B670	2313	>10000	21	100	110	>100

7.2.3. ANTIVIRAL ACTIVITY - HuPBMC INFECTIVITY ASSAYS

T1249 was directly compared to T20 in HuPBMC infectivity assays (Table 5, below), which represent a recognized surrogate *in vitro* system to predict plasma drug concentrations required for viral inhibition *in vivo*. These comparisons revealed that T1249 is more potent against all HIV-1 isolates tested to date, with all Vn/Vo = 0.1 (dose required to reduce virus titer by one log) values being reduced to sub-microgram concentrations. Many of the least sensitive clinical isolates to T20 exhibited 10-fold or greater sensitivity to T1249. It is noteworthy that HIV-1 9320, the isolate used in the HuPBMC SCID mouse model of infection, is 46-fold less sensitive to T20 than to T1249, indicating a very good correlation with the *in vivo* results.

**TABLE 5**

	Virus Isolate (HIV-1)	T20	T1249	Fold Difference
		Vn/Vo = 0.1 (ng/ml)	Vn/Vo = 0.1 (ng/ml)	
5	IIIB	250	80	3
	9320	6000	130	46
	301714 (subtype B, NSI)	8000	700	11
	302056 (subtype B, NSI)	800	90	9
10	301593 (subtype B, SI)	3500	200	18
	302077 (subtype A)	3300	230	14
	302143 (SI)	1600	220	7
	G691-2 (AZT-R)	1300	400	3

15                      7.2.4.      ANTIVIRAL ACTIVITY - T20 RESISTANT LAB ISOLATES

T1249 was directly compared to T20 in virus mediated cell-cell fusion assays conducted using chronically infected CEM cells mixed with uninfected Molt-4 cells (Table 6, below). T1249 was nearly 200-fold more potent than T20  
 20 against a T20-resistant isolate.

**TABLE 6**

	Virus Isolate	T20 (ng/ml)	n	T1249 (ng/ml)	n	Fold Difference
25	HIV-1 pNL4-3 SM (T20 Resistant)	405.3	3	2.1	3	193

In Magi-CCR-5 assays (see Table 7, below), T1249 is as much as 50,000-fold more potent than T20 against T20-resistant isolates such as pNL4-3 SM and pNL4-3 STM (Rimsky, L. and Matthews, T., 1998, J. Virol. 72:986-993).  
 30

**TABLE 7**

		T20		T1249			
5	Virus Isolate (HIV-1)	EC-50	Vn/Vo = 0.1	EC-50	Vn/Vo=0.1	EC-50 Fold Difference	Vn/Vo=0.1 Fold Difference
	pNL4-3	166	210	1	13	166	16
	pNL4-3 SM (T20-R)	90	900	4	11	23	82
10	pNL4-3 SM (T20-R) Duke	410	2600	4	11	103	236
	pNL4-3 STM (T20/T649-R)	>50 000	>5000 0	1	13	>50000	>3846

15 T1249 was directly compared to T20 in HuPBMC infectivity assays (see Table 8, below), evaluating differences in potency against a resistant isolate. T1249 is greater than 250-fold more potent than T20 against the resistant isolate pNL4-3 SM.

20

**TABLE 8**

25	T20		T1249	
	Virus Isolate (HIV-1)	Vn/Vo = 0.1 (ng/ml)	Vn/Vo = 0.1 (ng/ml)	Fold Difference
	pNL4-3	3500	30	117
	pNL4-3 SM (T20-R)	>10000	40	>250

30

#### 7.2.5. ANTIVIRAL ACTIVITY - IN VIVO SCID-HuPBMC MODEL

In vivo antiviral activity of T1249 was directly compared to T20 activity in the HuPBMC-SCID mouse model of HIV-1 9320 infection (FIG. 3). Two weeks after

reconstitution with HuPBMCs, mice were infected IP on day 0 with  $10^3$  TCID<sub>50</sub> HIV-1 9320 passed in PBMCs (AZT-sensitive isolate A018). Treatment with peptides was IP, bid, for total daily doses of 67 mg/kg (T20), 20 mg/kg (T1249), 6.7 mg/kg (T1249), 2.0 mg/kg (T1249), and 0.67 mg/kg (T1249), for 8 days beginning on day -1. The extent of infection in blood cells, splenocytes, lymph nodes, and peritoneal cells was assayed by quantitative co-culture with human PBMC blasts weekly for three consecutive weeks following animal exsanguinations and tissue harvest (day 7, approx. 12 to 18 hours following last drug treatment). Co-culture supernatants were evaluated for HIV-1 p24 antigen production as a measure of virus infection. Infectious virus was not detectable in the blood or lymph tissues of the T20-treated animals, although, virus was detected in the peritoneal washes and spleen preparation. All compartments were negative for infectious virus at the 6.7 mg/kg dose of T1249, indicating at least a 10-fold improvement over T20 treatment. At the 2.0 mg/kg dose of T1249, both the lymph and the spleen were completely free of detectable infectious virus, with a 2 log<sub>10</sub> reduction in virus titer in the peritoneal wash and a 1 log<sub>10</sub> reduction in virus titer in the blood, compared to infected controls. At the lowest dose of T1249, 0.67 mg/kg, the peritoneal washes and blood were equivalent to infected control; however, at least a 1 log<sub>10</sub> drop in infectious virus titer was observed in both the lymph and the spleen tissues. Overall, the results indicate that T1249 is between 30 and 100-fold more potent against HIV-1 9320, *in vivo*, under these conditions.

30

#### 7.2.6. PHARMACOKINETIC STUDIES - RAT

Cannulated rats were used to further define the pharmacokinetic profile of T1249. Male CD rats, 250-300 g,

were dosed IV through a jugular catheter with T1249 and T20 (FIGS. 4A-5). The resulting plasma samples were evaluated using fluorescence HPLC to estimate peptide quantities in extracted plasma. The beta-phase half-life and total AUC of T1249 was nearly three times greater than T20 (FIG. 5).

#### 7.2.7. CYTOTOXICITY

No overt evidence of T1249 cytotoxicity has been observed *in vitro*, as demonstrated in FIG. 6.

In addition, T1249 is not acutely toxic (death within 24 hours) at 167 mg/kg (highest dose tested) given IV through jugular cannula (0.3 ml over 2-3 min).

#### 7.2.8. DIRECT BINDING TO gp41 CONSTRUCT M41 Δ 178

T1249 was radiolabelled with  $^{125}\text{I}$  and HPLC-purified to maximum specific activity. T20 was iodinated in the same manner. Saturation binding of to M41Δ178 (a truncated gp41 ectodomain fusion protein lacking the T20 amino acid sequence) immobilized on microtitre plates at 0.5 mg/ $\mu\text{l}$  is shown in FIG.7. Nonspecific binding was defined as binding of the radioligand in the presence of 1  $\mu\text{M}$  unlabeled peptide. Specific binding was the difference between total and nonspecific binding. The results demonstrate that  $^{125}\text{I}$ -T1249 and  $^{125}\text{I}$ -T20 have similar binding affinities of 1-2 nM. Linear inverse Scatchard plots suggests that each ligand binds to a homogeneous class of sites.

The kinetics of  $^{125}\text{I}$ -T1249 and  $^{125}\text{I}$ -T20 binding was determined on scintillating microtitre plates coated with 0.5  $\mu\text{g}/\text{ml}$  M41Δ178. The time course for association and dissociation is shown in FIG.8. Dissociation of bound radioligand was measured following the addition of unlabeled peptide to a final concentration of 10  $\mu\text{M}$  in one-tenth of the total assay volume. Initial on- and off-rates for  $^{125}\text{I}$ -T1249

were significantly slower than those of  $^{125}\text{I}$ -T20. Dissociation patterns for both radioligands were unchanged when dissociation was initiated with the other unlabeled peptide (i.e.,  $^{125}\text{I}$ -T1249 with T20).

5 To further demonstrate that both ligands compete for the same target site, unlabeled T1249 and T20 were titrated in the presence of a single concentration of either  $^{125}\text{I}$ -T1249 or  $^{125}\text{I}$ -T20. Ligand was added just after the unlabeled peptide to start the incubation. The competition curves shown in FIG. 9 suggest that although both ligands have similar affinities, a  
10 higher concentration of either unlabeled T20 or T1249 is required to fully compete for bound  $^{125}\text{I}$ -T1249.

#### 7.2.9. DIRECT BINDING TO THE HR1 REGION OF GP41

15 Circular dichroism (CD) spectroscopy was used to measure the secondary structure of T1249 in solution (phosphate-buffered saline, pH 7) alone and in combination with a 45-residue peptide (T1346) from the HR1 (heptad repeat 1) binding region of gp 41. FIG. 14A illustrates the CD spectrum of T1249 alone in solution (10  $\mu\text{M}$ , 1°C). The  
20 spectrum is typical of peptides which adopt an alpha-helical structure. In particular, deconvolution of this spectrum using single value decomposition with a basis set of 33 protein spectra predicts the helix content of T1249 (alone in solution) to be 50%. FIG. 14B illustrates a representative  
25 CD spectrum of T1249 mixed with T1346. The closed squares (■) represent a theoretical CD spectrum predicted for a "non-interaction model" wherein the peptides are hypothesized to not interact in solution. The actual experimental spectrum (●) differs markedly from this theoretical "non-interaction  
30 model" spectrum, demonstrating that the two peptides do, indeed, interact, producing a measurable structural change which is observed in the CD spectrum.

7.2.10. PROTEASE PROTECTION OF THE T1249  
BINDING REGION WITHIN GP41

5 The susceptibility of the chimeric protein M41Δ178,  
described in Section 7.2.8 above, to proteinase-K digestion  
was determined and analyzed by polyacrylamide gel  
electrophoresis. The results are illustrated in FIG. 15.

When either M41Δ178 (untreated; FIG 15, lane 2) or  
T1249 (untreated; FIG. 15, lane 4) are incubated  
10 individually with proteinase K (FIG. 15, lanes 3 and 5,  
respectively), both are digested. However, when T1249 is  
incubated with M41Δ178 prior to addition of proteinase-K  
(FIG. 15, lane 7), a protected HR-1 fragment of approximately  
6500 Daltons results. Sequencing of the protected fragment  
15 demonstrates that it corresponds to a region of primary  
sequence located within the ectodomain of gp41. The  
protected fragment encompasses the soluble HR1 peptide  
(T1346) used in the CD studies described in Section 7.2.9  
above, and further contains an additional seven amino acid  
residues located on the amino terminus. This protection can  
20 be attributed to the binding of T1249 to a specific sequence  
of gp41 which is contained in the M41Δ178 construct.

8. EXAMPLE: RESPIRATORY SYNCYTIAL  
VIRUS HYBRID POLYPEPTIDES

25 The following example describes respiratory syncytial  
virus (RSV) hybrid polypeptides with enhanced pharmacokinetic  
properties. In addition, results are presented, below, which  
demonstrate that the RSV hybrid polypeptides represent potent  
inhibitors of RSV infection.

30

### 8.1. MATERIALS AND METHODS

#### 8.1.1. PEPTIDE-SYNTHESIS AND PURIFICATION

RSV polypeptides were synthesized using standard Fast Moc chemistry. Generally, unless otherwise noted, the peptides contained amidated carboxyl termini and acetylated amino termini. Purification was carried out by reverse phase HPLC.

#### 8.1.2. RESPIRATORY SYNCYTIAL VIRUS PLAQUE REDUCTION ASSAY

10 All necessary dilutions of peptides were performed in clean, sterile 96-well TC plate. A total of eleven dilutions for each peptide and one control well containing no peptide were assembled. The final concentration range of peptide started at 50µg/ml or 100µg/ml, with a total of eleven two-  
15 fold dilutions. The RSV was prepared at a concentration of 100PFU/well in 100µl 3% EMEM, as determined by a known titer of RSV. The virus is then added to all of the wells.

The media was removed from one sub-confluent 96-well plate of Hep2 cells. The material from the dilution plate was transferred onto the cell plates starting with row 1 and  
20 then transferring row 12, row 11, etc. until all rows were transferred. Plates were placed back into the incubator for 48 hours.

The cells were checked to ensure that syncytia were present in the control wells. Media was removed and  
25 approximately 50 µls of 0.25% Crystal Violet in methanol was added to each well. The wells were rinsed immediately in water to remove excess stain and allowed to dry. Using a dissecting microscope, the number of syncytia in each well was counted.

30

## 8.2. RESULTS

Pharmacokinetic studies with the RSV hybrid peptides T1301 (Ac-WQEWDEYDASISQVNEKINQALAYIREADELWA WF-NH<sub>2</sub>) and T1302  
5 (Ac-WQAWDEYDASISQVNEKINQALAYIREADELW AWF-NH<sub>2</sub>) containing enhancer peptide sequences demonstrated a greatly enhanced half-life relative to core peptide T786 (Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH<sub>2</sub>), as demonstrated in FIG. 10A-10B. Hybrid polypeptides T1301, T1302 and T1303  
10 (Ac-WQAWDEYDASISDVNEKINQALAYIREADELWEWF-NH<sub>2</sub>) also showed a greatly enhanced half-size relative to core peptide T1476 (Ac-DEYDASISQVNEKINQALAYIREADEL-NH<sub>2</sub>).

RSV hybrid polypeptides T1301, T1302 and T1303, as well as polypeptide T786 and T1293, were tested for their ability to inhibit RSV plaque formation of HEP2 cells. As indicated  
15 in FIGS. 11A and 11B, both the tested hybrid RSV polypeptides, as well as the T786 core polypeptide were able to inhibit RSV infection. Surprisingly, the T1293 hybrid polypeptide was also revealed to be a potent anti-RSV compound (FIG. 13).

20

## 9. EXAMPLE: LUTEINIZING HORMONE HYBRID POLYPEPTIDES

The example presented herein describes luteinizing hormone (LH) hybrid proteins with enhanced pharmacokinetic properties. The following LH hybrid peptides were  
25 synthesized and purified using the methods described above: core peptide T1323 (Ac-QHWSYGLRPG-NH<sub>2</sub>) and hybrid polypeptide T1324 (Ac-WQEWQKIQHWSYGLRPGWASLWEWF-NH<sub>2</sub>) which comprises the core polypeptide T1323 amino acid sequence coupled with enhancer peptides at its amino- and carboxy-termini. As  
30 demonstrated in FIG. 12A and 12B, the T1324 hybrid peptide exhibited a significantly increased half-life when compared

to the T1323 core peptide which lacks the enhancer peptide sequences.

10. EXAMPLE: PHARMACOLOGY OF HYBRID  
POLYPEPTIDE T1249

5 T1249, depicted in FIG. 13, is a hybrid polypeptide comprising enhancer peptide sequences linked to a core polypeptide derived from a mix of viral sequences. As demonstrated in the Example presented in Section 7 above, the T1249 hybrid polypeptide exhibits enhanced pharmacokinetic  
10 properties and potent *in vitro* as well as *in vivo* activity against HIV-1. In the example presented below, the pharmacological properties of T1249 in both rodent and primate animal models are further described.

15 10.1. MATERIALS AND METHODS

10.1.1. SINGLE-DOSE ADMINISTRATION TO RODENTS

T1249 was administered to Sprague-Dawley albino rats in a single dose administered by continuous subcutaneous infusion (SCI), subcutaneous (SC) injection or intravenous (IV) injection. Each treatment group consisted of nine rats  
20 per sex per group. The groups received sterile preparations of T1249 bulk drug substance at a dose of 0.5, 2.0, or 6.5 mg/kg by CSI. One group received 50mM carbonate-bicarbonate, pH 8.5, administered as a control. The peptides were given for 12 hours via a polyvinyl chloride/polyethylene  
25 catheter surgically implanted subcutaneously in the nape of the neck. Two groups received a single dose of T1249 at a dose of 1.2 or 1.5 mg/kg by subcutaneous injection into the intrascapular region. Two groups received a single dose of T1249 at a dose of 1.5 or 5 mg/kg via intravenous injection.  
30 The actual milligram amount of T1249 was calculated using the peptide content that was determined for the batch administered.

Endpoints for analysis included cageside observations (twice daily for mortality and moribundity), clinical observations, clinical laboratory parameters, body weight and necropsy. Blood samples were obtained by a sparse sampling technique over a 12 hour time period from three rats per sex per group at each of the following times: 0.5, 1, 2, 4, 6, 8, 19, and 12 hours after dose administration. Sample analysis was performed using a PcAb ECLIA assay (Blackburn, G. et al., 1991, Clin. Chem. 37:1534-1539; Deaver, D., 1995, Nature 377:758).

10 For plasma and lymphatic pharmacokinetic analysis of T1249 in rats, T1249 was prepared as a sterile solution in bicarbonate buffer and administered as a single dose, bolus intravenous injection into the lateral tail vein at a dose of 20 mg/kg. Blood was collected from the animal from an in-  
15 dwelling jugular catheter. Samples were collected immediately after dosing and at 5, 15, and 30 minutes, and 1, 2, 4, and 6 hours after drug administration. For the analysis of lymphatic fluids, samples were taken immediately before dosing and every 20 minutes for the first six hours  
20 after dosing. Lymphatic fluid was collected from a catheter placed directly into the thoracic lymphatic duct as previously described (Kirkpatrick and Silver, 1970, The Journal of Surgical Research 10:147-158). The concentrations of T1249 in plasma and lymphatic fluid were determined using  
25 a standard T1249 Competitive ELISA assay (Hamilton, G. 1991, p. 139, in "Immunochemistry of Solid-Phase Immunoassay," Butler, J., ed., CRC Press, Boston).

#### 10.1.2. SINGLE-DOSE ADMINISTRATION TO PRIMATES

30 Sterile preparations of T1249 bulk drug substance were administered to cynomolgus monkeys in single doses administered by subcutaneous (SC), intramuscular (IM) or intravenous (IV) injection. In a sequential crossover

design, one group of animals consisting of two per sex received a single bolus dose of T1249 by IV (0.8 mg/kg), IM (0.8 mg/kg) or SC (0.4, 0.8, and 1.6 mg/kg) injection. A washout period of at least three days separated each dosing day. Lyophilized T1249 was reconstituted in sterile phosphate buffered saline pH 7.4 immediately prior to dosing. The actual milligram amount of test article was calculated using the peptide content that was determined for the batch administered.

Endpoints for analysis included cageside observations, physical examinations and body weight. For the IV phase of the study, blood samples were collected into heparinized tubes at the following time points: immediately after dosing, 0.25, 0.5, 1.5, 3, 6, 12, and 24 hours after dosing. For the IM and SC phases of the study blood samples were collected in heparinized tubes from each animal at the following time points: 0.5, 1, 2, 3, 6, 12, and 24 hours after dosing. Plasma samples were prepared within one hour of collection and flash frozen in liquid nitrogen. Samples analysis was performed using a PcAb ECLIA assay (Blackburn, G. et al., 1991, Clin. Chem. 37:1534-1539; Deaver, D., 1995, Nature 377:758).

#### 10.1.3. BRIDGING PHARMACOKINETIC STUDY

Six male cynomolgus monkeys were randomly assigned to three groups consisting of two animals per group. All doses of T1249 were given by bolus subcutaneous injection. The study was divided into two sessions. In Session 1, animals in groups 1, 2 and 3 received a sterile preparation of T1249 bulk drug substance (*i.e.*, bulk T1249 dissolved in carbonate-bicarbonate, pH 8.5) twice daily for four consecutive days (Study Days 1-4) at doses of 0.2, 0.6 and 2.0 mg/kg/dose, respectively. A ten day washout period separated Session 1 and Session 2. In Session 2, animals in groups 1, 2, and 3

received a sterile preparation of T1249 drug product (i.e., in aqueous solution, pH 6.5, plus mannitol) twice daily for four consecutive days (Study Days 15-18) at doses of 0.2, 0.6 and 2.0 mg/kg/dose, respectively.

5 Blood samples for pharmacokinetic analyses were collected on Study Days 1 and 15 to assess single-dose pharmacokinetic parameters, and on Study Days 4 and 18 to assess steady-state plasma pharmacokinetic parameters. Samples were collected at the following times: immediately pre-dose, and 0.5, 1.5, 3.0, 4.0, 6.0, 8.0 and 12.0 hours  
10 post-dose. Animals were monitored during Sessions 1 and 2 for clinical signs and changes in body weight.

## 10.2. RESULTS

### 10.2.1. PHARMACOKINETICS OF T1249

#### 15 ADMINISTERED TO RATS

Rat models were used to perform an initial assessment of plasma pharmacokinetics and distribution of T1249. For animals in all dose groups, there were no changes in body weight, physical observations, hematology and clinical chemistry parameters or macroscopic pathology observations  
20 related to the administration of T1249.

Rats that received T1249 by CSI achieved steady-state plasma peptide concentrations approximately four hours after administration. Both the steady-state concentration in plasma ( $C_{p_{ss}}$ ) and calculated area under the plasma  
25 concentration versus time curve (AUC) were directly proportional to the administered dose, indicating that T1249 displays linear pharmacokinetics within the tested dose range of 0.5 to 6.5 mg/kg. Both the calculated pharmacokinetic parameters and the plasma concentration versus time curves  
30 for the CSI route of administration are presented in Table 9 and in FIG. 16A, respectively.

TABLE 9

Parameter	Dose Groups		
	0.5 mg/kg	2.0 mg/kg	6.5 mg/kg
5 $C_{p_{ss}}$ ( $\mu\text{g/ml}$ )	0.80	2.80	10.9
$AUC_{(0-12h)}$ ( $\mu\text{g}\cdot\text{h/ml}$ )	7.99	25.9	120

Administration of T1249 by bolus IV injection resulted in linear dose-dependent pharmacokinetics within the doses tested. In contrast, exposure to T1249 by SC injection was not dose-dependent within the dose range studied. The calculated pharmacokinetic parameters and plasma concentration versus time curves for both SC and IV administration of T1249 are shown in Table 10 and FIG. 16B respectively.

TABLE 10

Parameter	Dose Groups/Administration			
	(SC)	(SC)	(IV)	(IV)
20 $t_{1/2}$ (hours)	1.2 mg/kg	15 mg/kg	1.5 mg/kg	5.0 mg/kg
$t_{1/2}$ (hours)	2.02	2.00	2.46	1.86
$t_{max}$ (hours)	1.09	1.88	-	-
$C_{max}$ ( $\mu\text{g/ml}$ )	6.37	21.5	15.7	46.3
25 $AUC_{(0-12h)}$ ( $\mu\text{g}\cdot\text{h/ml}$ )	27.0	107	45.6	118
$AUC_{(0-\infty)}$ ( $\mu\text{g}\cdot\text{h/ml}$ )	27.6	110	47.1	120

30 The bioavailability of T1249 administered to rats by subcutaneously was determined relative to IV administration. The results are shown in Table 11 below. At low dose

(1.2 mg/kg) T1249 exhibited a relative bioavailability ( $F_R$ ) of 73% for subcutaneous administration. Relative bioavailability was 30% when high-dose (15 mg/kg) administration of T1249 concentration was greater than the concentration that inhibits 90% ( $IC_{90}$ ) of HIV infectivity for the full 12 hours of the study at all doses examined.

TABLE 11

	Route	Dose (mg/kg)	AUC <sub>(0-∞)</sub> ( $\mu\text{g}\cdot\text{h}/\text{ml}$ )	Normalized AUC <sub>(0-∞)</sub> ( $\mu\text{g}\cdot\text{h}/\text{ml}$ )	$F_R$ (%)
10	Low Dose				
	SC	1.2	27.6	34.5 <sup>(a)</sup>	73
	IV	1.5	47.1	-	-
	High Dose				
15	SC	15	110	36.5 <sup>(b)</sup>	30
	IV	5	120	-	-

<sup>(a)</sup> Normalized from a 1.2 mg/kg dose to a 1.5 mg/kg dose by multiplying AUC<sub>(0-∞)</sub> by 1.25.

<sup>(b)</sup> Normalized from a 15 mg/kg dose to a 5 mg/kg dose by dividing AUC<sub>(0-∞)</sub> by 3.

The kinetic data for both plasma and lymph concentrations of T1249 are illustrated in FIG. 16C and tabulated below in Table 12. T1249 rapidly penetrated into the lymphatic system and equilibrated with the plasma reservoir of drug within approximately one hour after administration. Following equilibration between the two compartments, plasma and lymph levels of drug were comparable out to three hours post-dosing in four out of five animals. One animal had consistently lower concentrations of T1249 in the lymph than the other animals, however this animal's lymph elimination profile was indistinguishable from other members of the group. Comparison of the elimination phase half-life ( $t_{1/2}$ ) for plasma and lymph suggest that the transit of T1249 between these two compartments is a diffusion-controlled process. After three hours, there appeared to be a second,

more rapid elimination phase from the lymphatic system. This difference could be mechanism-based (e.g., due to redistribution or accelerated peptide degradation in the lymph) or due to other factors. The concentration of T1249 in lymphatic fluid six hours post-injection is greater than the  $IC_{50}$  for viral infectivity for common laboratory strains and for primary clinical isolates of HIV-1.

The extent of penetration of T1249 into cerebrospinal fluid (CSF) was also assessed. T1249 concentrations were below the limit of detection (LOD; 2.0 ng T1249/ml CSF) at all measurable time points, indicating that T1249 does not penetrate the central nervous system after a single dose administration.

TABLE 12

Parameter	T1249	
	Plasma	Lymph
$t_{1/2}$ , elimination(hours)	2.6±0.41	1.3±0.27
$C_{max}$ (µg/ml)	291	133 <sup>(a)</sup> /155 <sup>(b)</sup>
$AUC_{(0-6h)}$ (µg•h/ml)	506	348 <sup>(a)</sup> /411 <sup>(b)</sup>
$AUC_{(0-\infty)}$ (µg•h/ml)	598	390 <sup>(a)</sup> /449 <sup>(b)</sup>
Cl (ml/h)	7.8	11.5

<sup>(a)</sup> Calculated averages include one animal (Rat #1) that exhibited significantly lower lymph concentrations but a similar kinetic profile by comparison to the other animals in the group.

<sup>(b)</sup> Calculated averages that exclude Rat #1.

#### 10.2.2. PHARMACOKINETICS OF T1249 ADMINISTERED TO PRIMATES

Primate models were used to evaluate the relationship between dose level and various pharmacokinetic parameters associated with the parenteral administration of T1249. Plasma concentrations greater than 6.0 µg/ml of T1249 were

achieved by all routes of administration and quantifiable levels (i.e., levels greater than 0.5  $\mu\text{g/ml}$ ) were detected at 24 hours after SC and IV administration. The elimination  $t_{1/2}$  was comparable for all routes of administration (5.4 hours, 4.8 hours and 5.6 hours for IV, SC and IM administration, respectively). Plasma concentrations of T1249 that exceed the  $\text{IC}_{50}$  values for laboratory strains and clinical isolates of HIV-1 were observed at all measured time points throughout the 24 hour sampling period.

A comparison of the data obtained for the parenteral administration of 0.8 mg/kg T1249 via all routes of administration (SC, IV, and IM) is presented in FIG. 17A. FIG. 15B illustrates a comparison of the data obtained from SC injection at three different dose levels of T1249 (0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg). The insert in FIG. 17B contains a plot of the calculated AUC versus administered dose.

T1249 displays linear pharmacokinetics in cynomolgus monkeys following SC administration within the range of administered doses, indicating that saturation of the clearance mechanism or mechanisms has not occurred within this range. A summary of the pharmacokinetic data following parenteral administration of T1249 to cynomolgus monkeys is provided in Table 13, below. A comparison of the plasma AUC values indicates that, relative to intravenous administration, the bioavailability of T1249 is approximately 64% when given by intramuscular injection and 92% when given by subcutaneous injection.

Table 13

5	Parameter	Administration Route (Dose Level, mg/kg)				
		SC (0.4)	SC (0.8)	SC (1.6)	IM (0.8)	IV (0.8)
	$t_{1/2, \text{terminal}}$ (h)	6.23±0.52	4.83±0.48	5.55±0.92	5.57±0.24	5.35±0.95
	$t_{\text{max}}$ (h)	3.97±1.18	4.58±1.45	4.72±1.81	2.32±0.43	-
	$C_{\text{max}}$ (µg/ml)	3.17±0.09	6.85±1.01	13.3±2.55	6.37±1.69	26.7±0.25
	$AUC_{(0-24)}$	37.5±6.6	8.12±11.4	168±34.0	56.4±12.3	87.4±25.0
10	(µg•h/ml)					
	$AUC_{(0-\infty)}$	40.9±8.2	85.3±13.6	181±44.0	59.5±13.1	92.5±25.0
	(µg•h/ml)					
	$F_R$ (%)	-	92.3	-	64.4	-

15

10.2.3. BRIDGING PHARMACOKINETIC STUDY

Bridging pharmacokinetic studies were performed in order to compare the plasma pharmacokinetic profiles of the T1249 bulk drug substances used in the nonclinical trials described above to the formulated T1249 drug product which would be administered to an actual subject or patient, e.g., to treat HIV infection. The study was designed as a parallel group, one-way, cross-over comparison of three dose levels of T1249 bulk drug substance and three dose levels of formulated drug product. Plasma pharmacokinetics were assessed after single-dose administration and after steady state was achieved.

25

Administration of T1249 by subcutaneous injection resulted in measurable levels of peptide in all dose groups. The plasma concentration-time curves were roughly parallel within all dose groups following the initial dose (Days 1 and 15) and at steady state (Days 4 and 18) for both T1249 bulk drug substance and formulated T1249 drug product.

30

Furthermore  $AUC_{(0-12hr)}$  values varied in direct proportion to the dose level for both drug formulations. Calculated  $AUC_{(0-12hr)}$

values for the drug product ranged from 43% to 80% of the  $AUC_{(0-12hr)}$  values calculated for drug substance following single dose administration, and from 36% to 71% at steady state.

5 T1249 bulk drug substance and drug product demonstrated similar pharmacokinetic profiles in cynomolgus monkeys following bolus subcutaneous administration at the dose levels and dose volume tested. A direct comparison of the shapes of the plasma concentration-time curves in the present study and the shapes of curves from a previous study in  
10 cynomolgus monkeys suggests that there is a depot effect when T1249 is administered by subcutaneous injection. This is suggested by the increases in time at which maximal plasma concentration ( $t_{max}$ ) is achieved and  $t_{1/2}$ .

These results indicate that the formulation of bulk drug substance used in the pharmacology program yields comparable  
15 AUC values and other kinetic parameters to those observed following the administration of the formulated drug product. These observations indicate that clinical administration of T1249 will result in total patient exposure to T1249.

20 11. EXAMPLE: ISOLATION OF A NOVEL CORE  
POLYPEPTIDES WITH ANTIVIRAL ACTIVITY  
FOR A T649 RESISTANT HIV-1 ISOLATE

Described herein, in one particular, but non-limiting example, a modified core peptide is generated that exhibits  
25 antiviral activity against HIV strains resistant to an unmodified, "parent" core peptide.

The peptide T649 shown in Table 2 is a peptide derived from a region of the HIV-1 gp41 protein referred to herein as HR2. In studies of HIV-1 variants resistant to T649, isolation and sequencing of the nucleic acid encoding the HR2  
30 region of the resistant variants' gp41 peptide reveals a mutation that results in a single mutation within this

region: a change from an asparagine (N) to a lysine (K) residue.

Using the result, a new polypeptide, referred to herein as DP397, was synthesized that contains the T649 amino acid  
5 sequence into which the above-noted N-to-K mutation has been introduced. The T649 and DP397 peptides are shown below, with the single amino acid difference between the two peptides depicted in bold:

T649: WMEWDREIN**NY**TSLIHSLIEESQNQQEKNEQELL  
10 DP397: WMEWDREIN**KY**TSLIHSLIEESQNQQEKNEQELL

It is noted that the difference between T649 and DP397 falls within a potential N-glycosylation site (underlined). Thus, the mutation in the gp41 of the T649-resistant strains  
15 had abolished this potential N-glycosylation site.

The DP397 core polypeptide exhibits anti-viral activity against the HIV-1 variants that are resistant to the T649 peptide. In particular, the DP397 peptide exhibited markedly increased antiviral activity, as assayed by the Magi-CCR-5  
20 infectivity assay described in Section 7.1.7, above, against four HIV-1 variants. Further, the DP397 peptide was also found, in certain experiments, to exhibit increased antiviral activities against these strains relative to the T1249 peptide.

FIGS. 18A-D show the number of infected cells exposed to  
25 T649 resistant variants as a function of the peptide concentration for T649, DP397, and T1249. Specifically, FIGS. 18A-B show data from experiments using the T649 resistant HIV-1 strains referred to herein as RF-649 and DH012-649, respectively. These strains derived from HIV-1<sub>RF</sub>  
30 and HIV-1<sub>DH012</sub> isolates, respectively, which were passed through cell cultures in the presence of T649 to produce T649 resistant variants.

FIGS. 18C-D show data from experiments using engineered T649 resistant HIV-1 strains referred to herein as 3'ETVQQQ and SIM-649, respectively. The strain 3'ETVQQQ was obtained from an HIV-1<sub>LAI</sub> clone that was molecularly mutagenized to contain the amino acid sequence ETVQQQ, in place of GIVQQQ in the HR1 domain of the gp41 protein. HR1 is a region of the HIV-1 gp41 protein to which the HR2 domain and the T649 peptide bind. The strain SIM-649 was obtained from an HIV-1<sub>LAI</sub> clone that was molecularly mutagenized to contain the amino acid sequence SIM, in place of GIV, in the HR1 domain of the gp41 protein, and subsequently passed through cell cultures in the presence of T649 to produce a T649 resistant variant.

The DP397 peptide exhibits markedly increased inhibition of HIV-1 infection compared to T649 for all four strains examined. Further, the DP397 peptide exhibits increased inhibition of HIV-1 infection compared to T1249 for the RF-649 strain (FIG. 18A) and, at higher concentrations, for the DH012-649 strain (FIG. 18B).

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide.
- 5 2. The hybrid polypeptide of Claim 1, wherein the enhancer peptide sequence comprises: WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXX, XXXWXX, XXWXX, XWXWX, WXXW, WXXXWXXW, WXXXW, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXXXW, XWXWXXX, XWXWXX, XWXWX, XWXW, WXXWXXXW or XWXXXW.
- 10 3. The hybrid polypeptide of Claim 1 wherein the enhancer peptide sequence comprises WQEWEQKI or WASLWEWF.
4. The hybrid polypeptide of Claim 1, wherein the enhancer peptide sequence is linked to the amino-terminal end  
15 of the core polypeptide.
5. The hybrid polypeptide of Claim 4, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.
- 20 6. The hybrid polypeptide of Claim 1, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.
- 25 7. The hybrid polypeptide of Claim 1 wherein the core polypeptide is a therapeutic reagent.
8. The hybrid polypeptide of Claim 1 wherein the core polypeptide is a bioactive peptide, a growth factor, cytokine, differentiation factor, interleukin, interferon,  
30 colony stimulating factor, hormone or angiogenic factor amino acid sequence.

9. The hybrid polypeptide of Claim 1, wherein the core polypeptide comprises the following amino acid sequence:

YTSLIHSLIEESQNQQEKNEQEELLELDK; LEENITALLEEAAQIQQEKKNMYELQKLNS;  
 LEANISQSLEQAQIQQEKKNMYELQKLNS; NNYTSLIHSLIEESQNQQEKNEQEELLEL;  
 5 DFLEENITALLEEAAQIQQEKKNMYELQKL; RYLEANISQSLEQAQIQQEKKNMYELQKL;  
 RYLEANITALLEEQAQIQQEKNEYELELDK; NNYTSLIHSLIEESQNQQEKNEQEELLELDK;  
 TALLEQAQIQQEKNEYELELDK;  
 TALLEQAQIQQEKNEYELELDK;  
 TALLEQAQIQQEKNEYELELDK;  
 10 TALLEQAQIQQEKIEYELELDK;  
 TALLEQAQIQQEKIEYELELDK;  
 TALLEQAQIQQEKIEYELELDK;  
 TALLEQAQIQQEKIEYELELDK;  
 TALLEQAQIQQEKIEYELELDK;  
 TALLEQAQIQQEKIEYELELDK;  
 TALLEQAQIQQEKIEYELELDK;  
 15 TALLEQAQIQQEKAEYELELDK;  
 TALLEQAQIQQEKNEYELELDK;  
 TALLEQAQIQQEKGEYELELDK;  
 TALLEQAQIQQEKAEYELELDK;  
 TALLEQAQIQQEKNEYELELDK;  
 20 TALLEQAQIQQEKGEYELELDK;  
 TALLEQAQIQQEKAEYELELDK;  
 TALLEQAQIQQEKNEYELELDK;  
 TALLEQAQIQQEKGEYELELDK;  
 DEFDAISQVNEKINQSLAFIRKSDELL;  
 DEYDAISQVNEKINQALAYIREADEL;  
 25 DEYDAISQVNEEINQALAYIRKADEL; DEFDESISQVNEKIEESLAFIRKSDELL;  
 DEFDESISQVNEKIEESLAFIRKSDEL; or  
 QHWSYGLRPG.

10. The hybrid polypeptide of Claim 9, wherein the  
 30 enhancer peptide sequence is linked to the amino-terminal end  
 of the core polypeptide.

11. The hybrid polypeptide of Claim 10, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

5 12. The hybrid polypeptide of Claim 9, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.

13. The hybrid polypeptide of Claim 9, wherein the enhancer peptide sequence comprises WQEWQKI or WASLWEWF.  
10

14. The hybrid polypeptide of Claim 9, wherein the hybrid polypeptide comprises the amino acid sequence:  
WQEWQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF,  
WQEWQKITALLEQAQIQQEKIEYELQKLIEWEWF or  
15 VYPSDEYDASISQVNEEINQALAYIRKADELLENV.

15. The hybrid polypeptide of Claim 14, further comprising an amino terminal acetyl group and a carboxy terminal amido group.

20 16. A core polypeptide comprising:  
YTSLIHSLIEESQNQQEKNEQELLELDK; LEENITALLEEQAQIQQEKKNMYELQKLNS;  
LEANISQSLEQAQIQQEKKNMYELQKLNS; NNYTSLIHSLIEESQNQQEKNEQELLEL;  
DFLEENITALLEEQAQIQQEKKNMYELQKL; RYLEANISQSLEQAQIQQEKKNMYELQKL;  
RYLEANITALLEEQAQIQQEKNEYELQKL; NNYTSLIHSLIEESQNQQEKNEQELLELDK;  
25 TALLEQAQIQQEKNEYELQKLDK;  
TALLEQAQIQQEKNEYELQKLDE;  
TALLEQAQIQQEKNEYELQKLIE;  
TALLEQAQIQQEKIEYELQKLDK;  
TALLEQAQIQQEKIEYELQKLDE;  
30 TALLEQAQIQQEKIEYELQKLIE;  
TALLEQAQIQQEKIEYELQKLE;  
TALLEQAQIQQEKIEYELQKLAK;

TALLEQAQIQQEKIEYELQKLAE;  
TALLEQAQIQQEKA EYELQKLE;  
TALLEQAQIQQEKNEYELQKLE;  
TALLEQAQIQQEKGEYELQKLE;  
5 TALLEQAQIQQEKA EYELQKLAK;  
TALLEQAQIQQEKNEYELQKLAK;  
TALLEQAQIQQEKGEYELQKLAK;  
TALLEQAQIQQEKA EYELQKLAE;  
TALLEQAQIQQEKNEYELQKLAE;  
TALLEQAQIQQEKGEYELQKLAE;  
10 DEFDASISQVNEKINQSLAFIRKSDELL;  
DEYDASISQVNEKINQALAYIREADEL;  
DEYDASISQVNEEINQALAYIRKADEL; DEFDESISQVNEKIEESLAFIRKSDELL;  
DEFDESISQVNEKIEESLAFIRKSDEL; or  
QHWSYGLRPG.

15

17. The core polypeptide of Claim 16, further comprising an amino terminal acetyl group and a carboxy terminal amido group.

20

18. A method for enhancing the pharmacokinetic properties of a core polypeptide comprising linking a consensus enhancer peptide sequence to a core polypeptide to form a hybrid polypeptide, such that, when introduced into a living system, the hybrid polypeptide exhibits enhanced pharmacokinetic properties relative those exhibited by the  
25 core polypeptide.

19. The method of Claim 18 wherein the core polypeptide is a therapeutic reagent.

30

20. The method of Claim 18 wherein the core polypeptide is a bioactive peptide, growth factor, cytokine,

differentiation factor, interleukin, interferon, colony  
stimulating factor, hormone or angiogenic factor.

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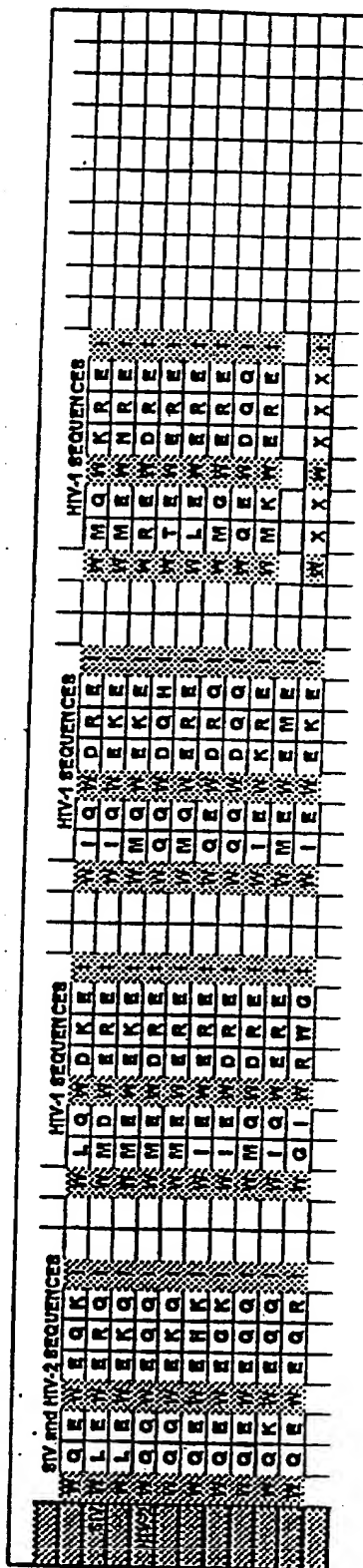


FIGURE 2A

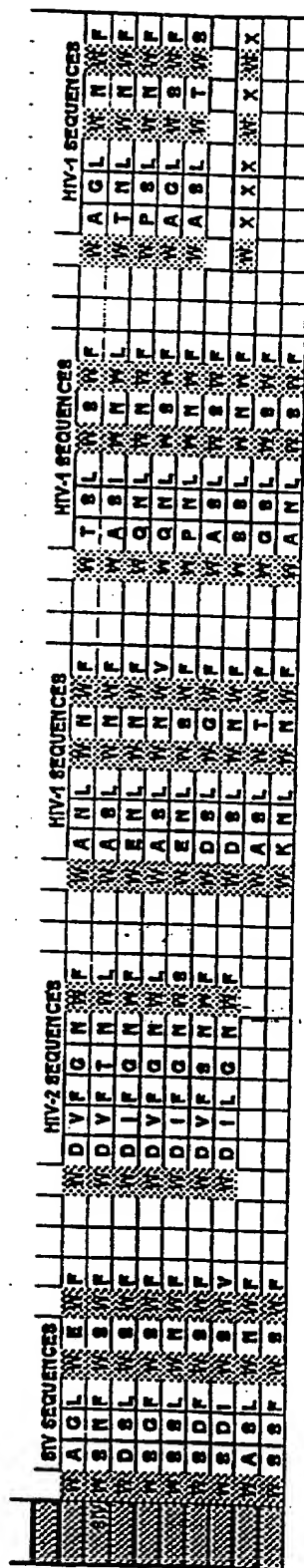


FIGURE 2B

3/27

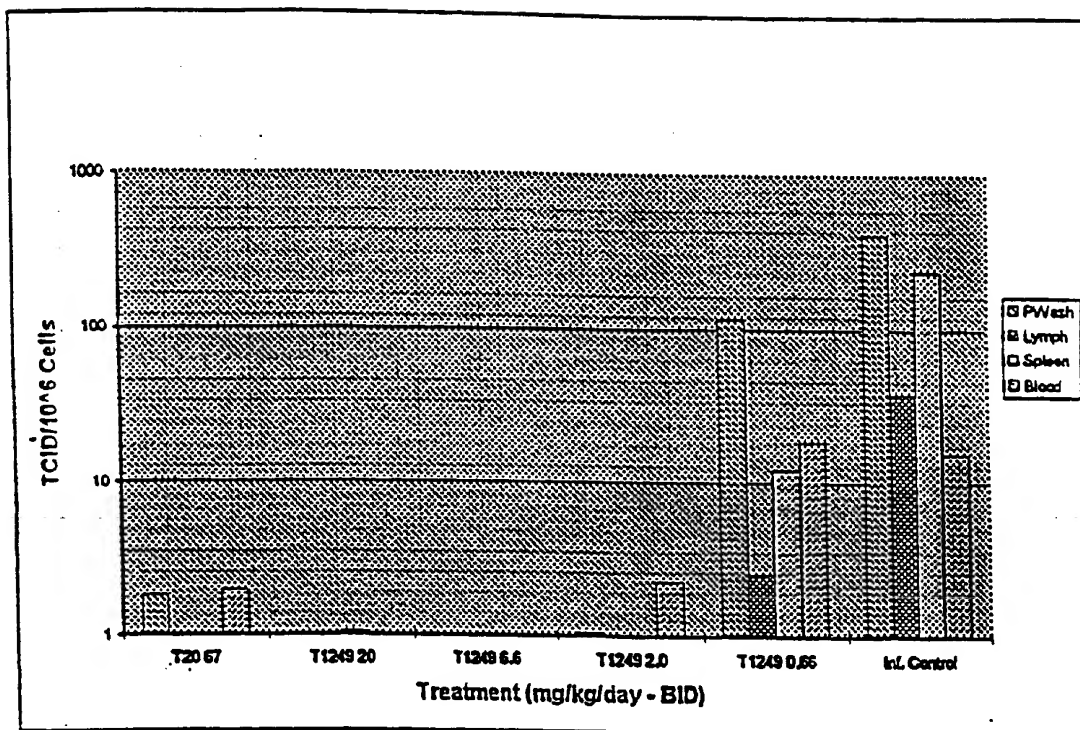


FIGURE 3

4/27

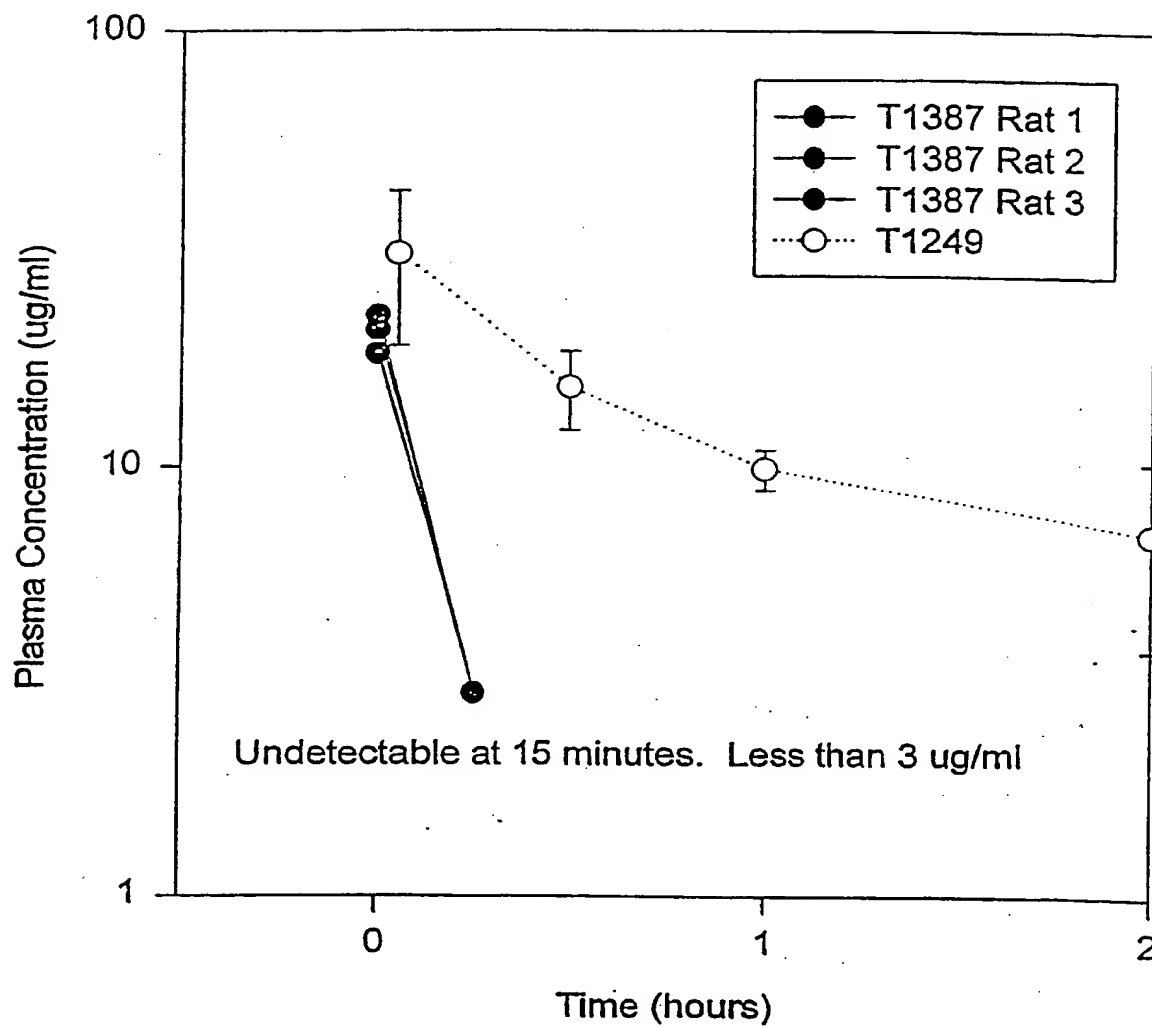


FIGURE 4A

5/27

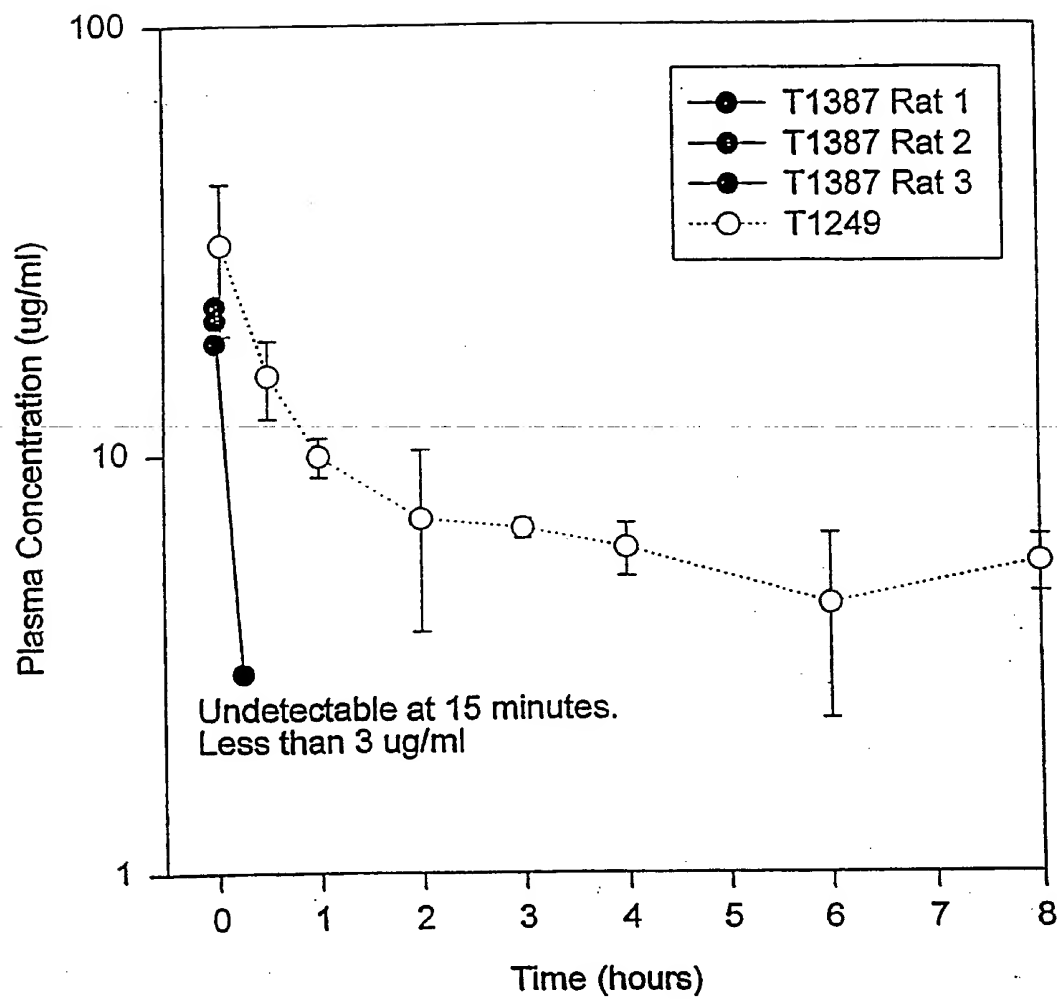
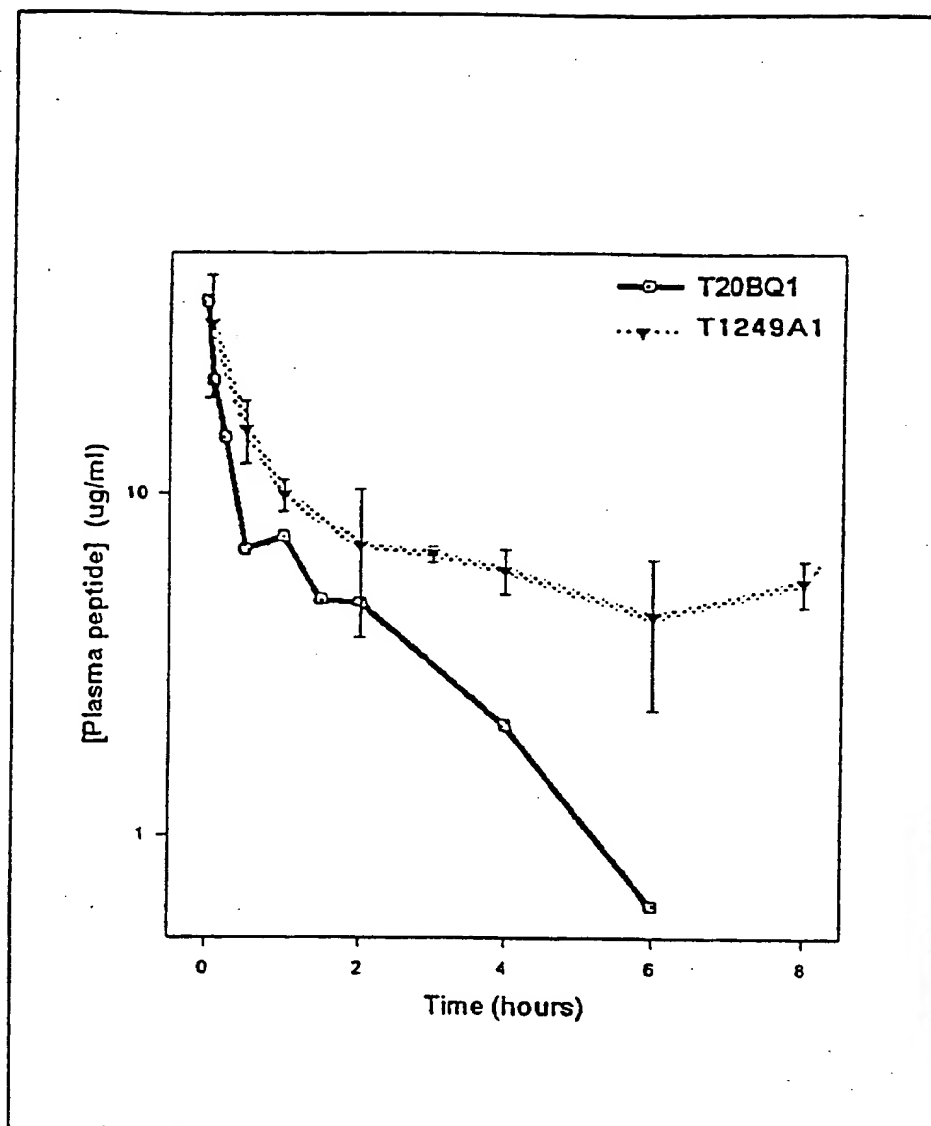


FIGURE 4B



Pharmacokinetic Parameters	T20BQ1	T1249A1
Dose (mg/kg IV)	2.5	2.5
Detection method	Fluorescence HPLC	Fluorescence HPLC
T <sub>1/2α</sub> (h)	1.6	4.71
Cl <sub>p</sub> (ml/h)	27.94	9.62
AUC <sub>(0-∞)</sub> (ug·h/ml)	26.12	71.43

FIGURE 5

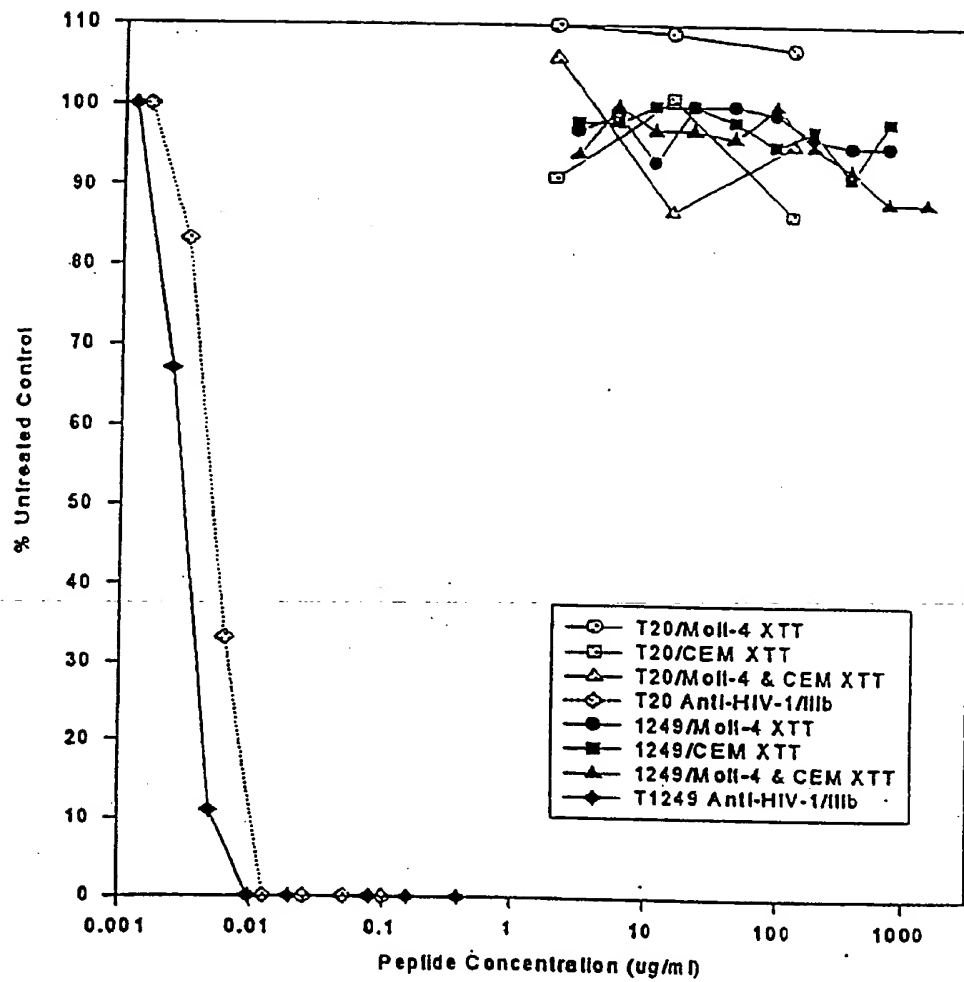


FIGURE 6

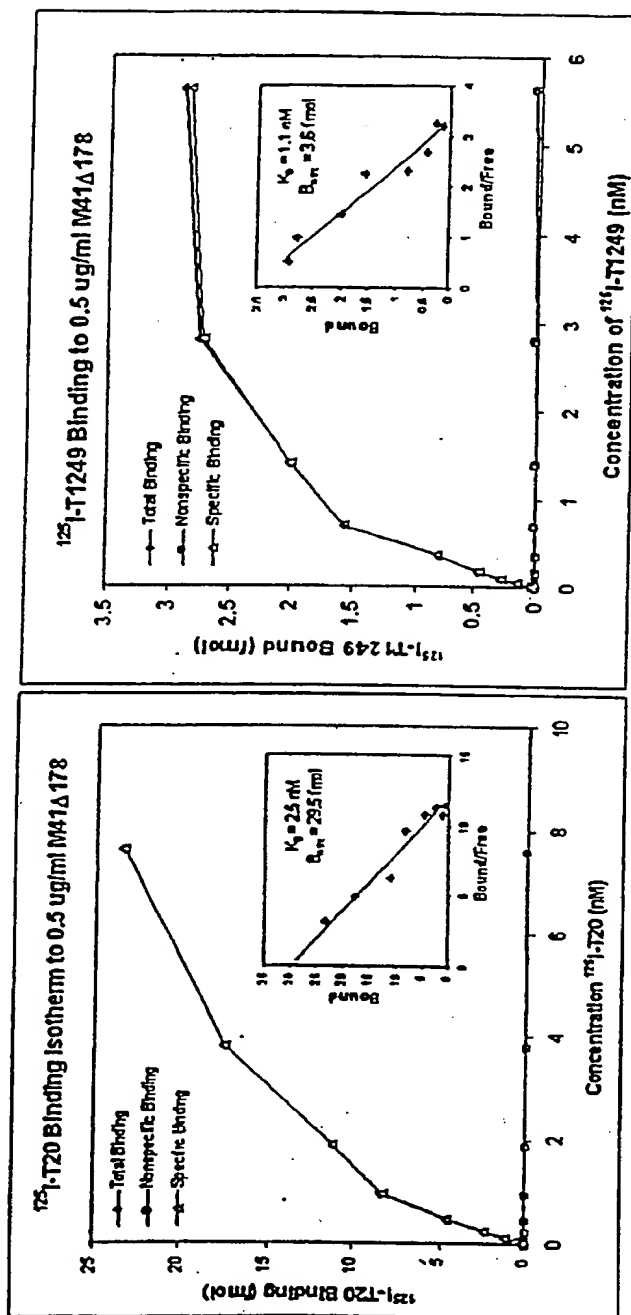


FIGURE 7

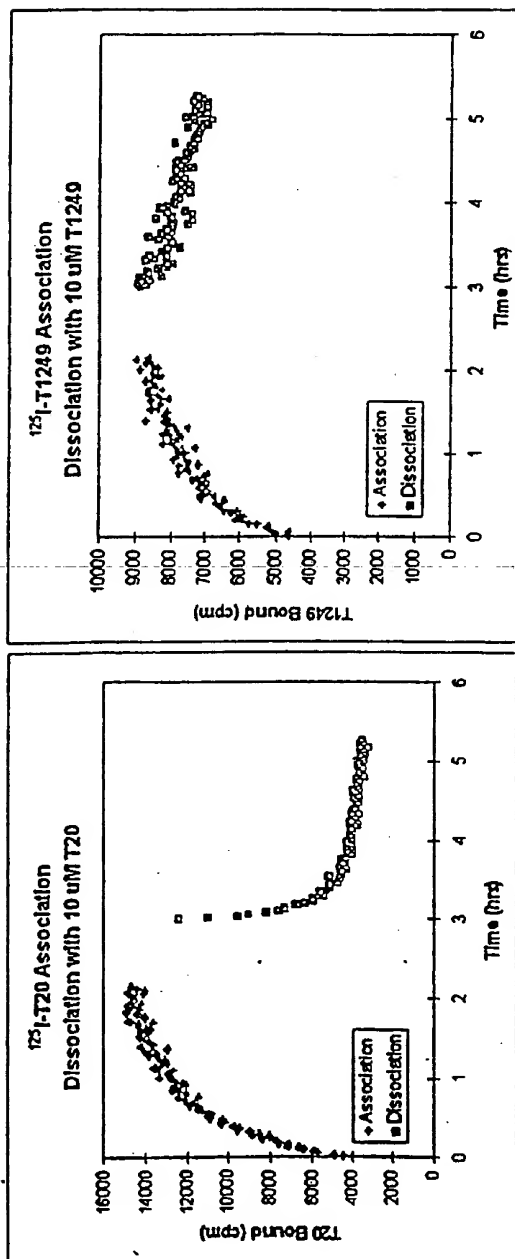


FIGURE 8

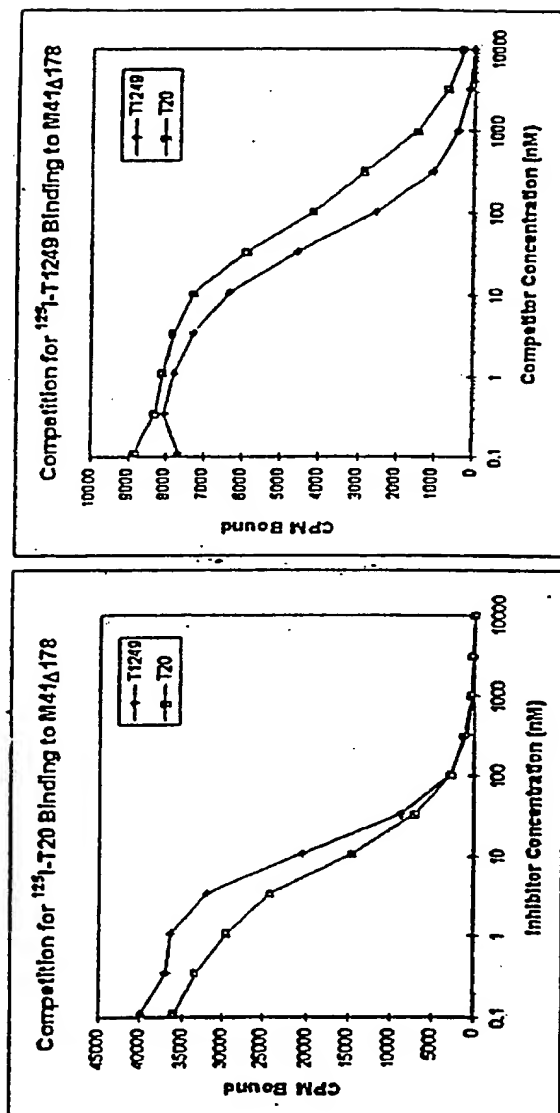


Figure 9

11/27

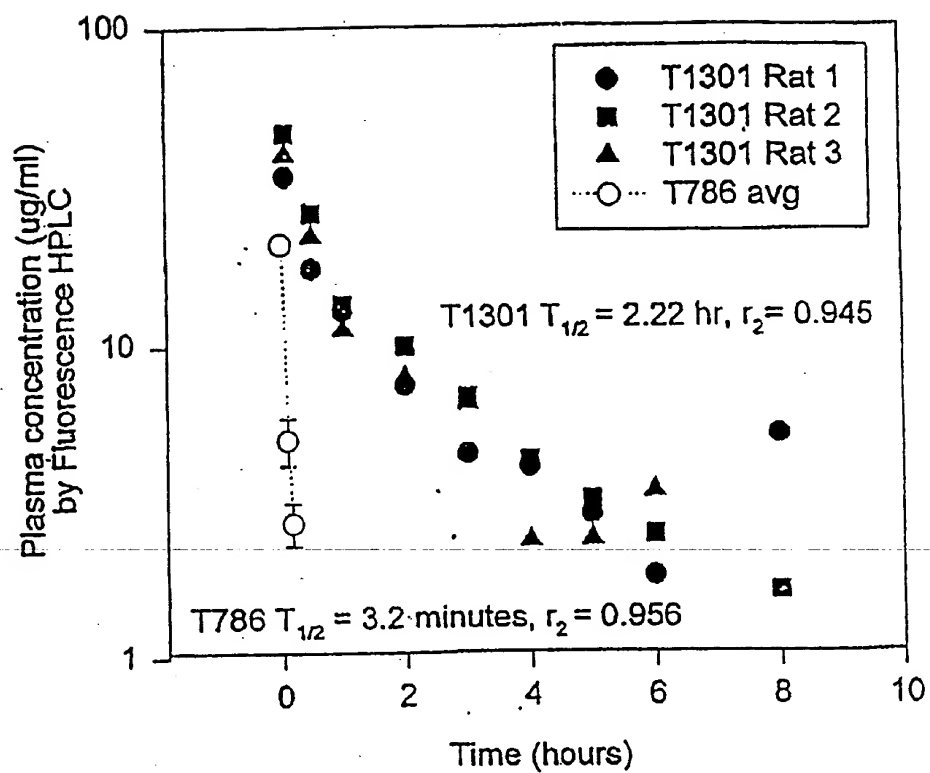


FIGURE 10A

12/27

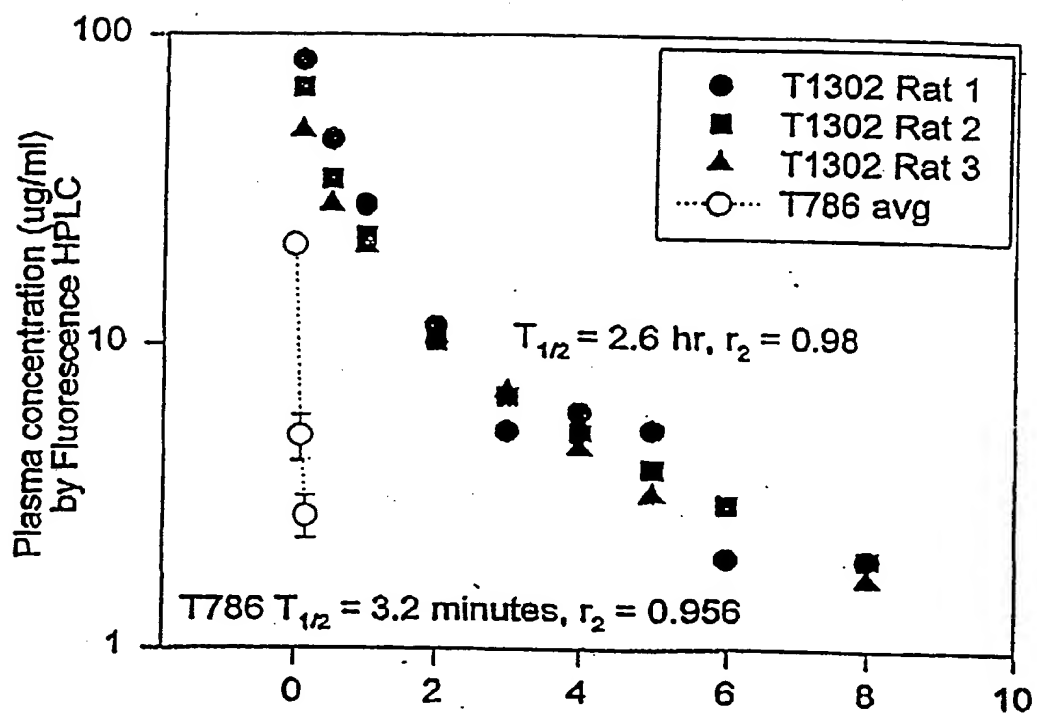
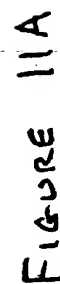


FIGURE 10B



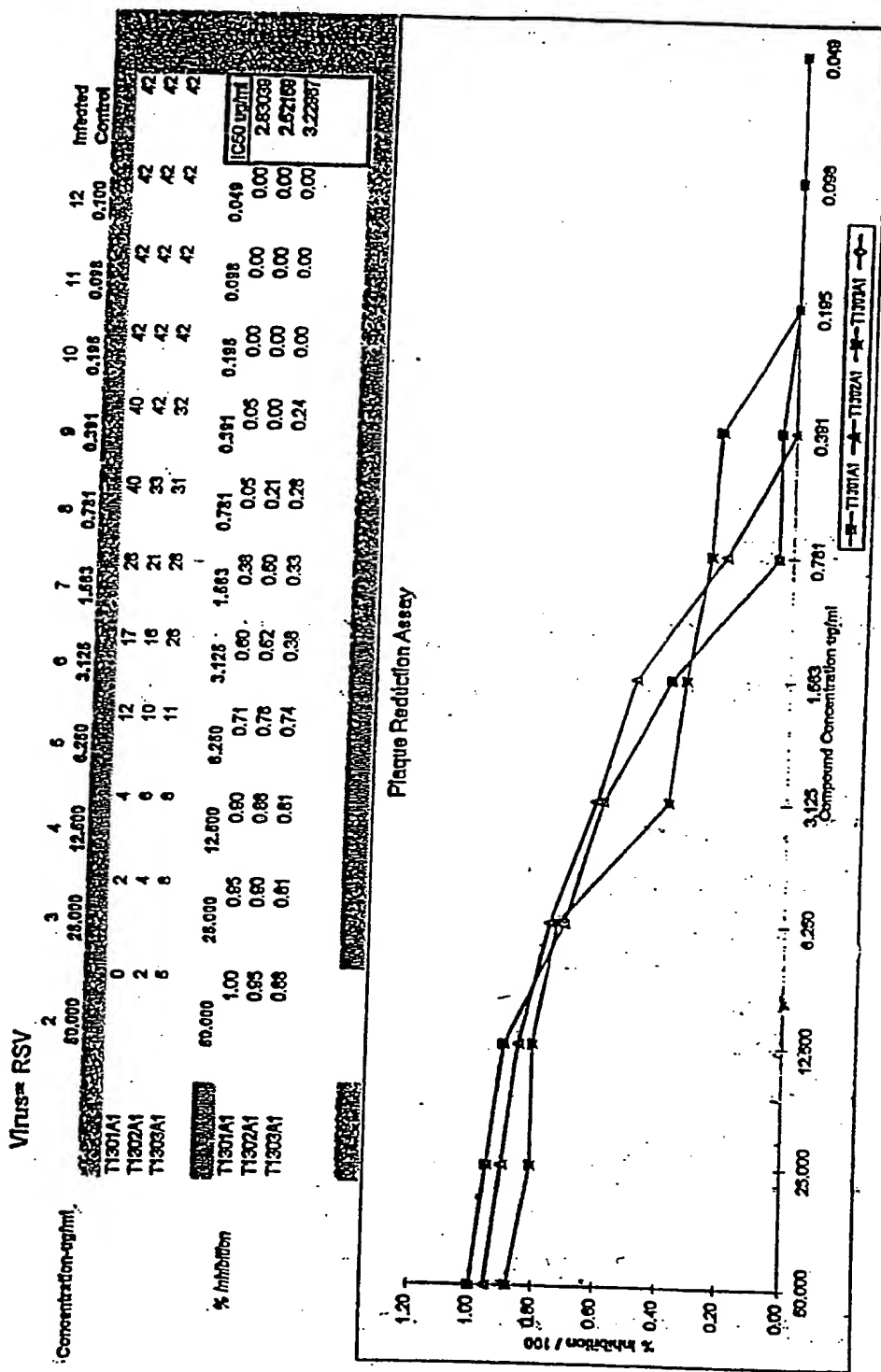


FIGURE 11 B

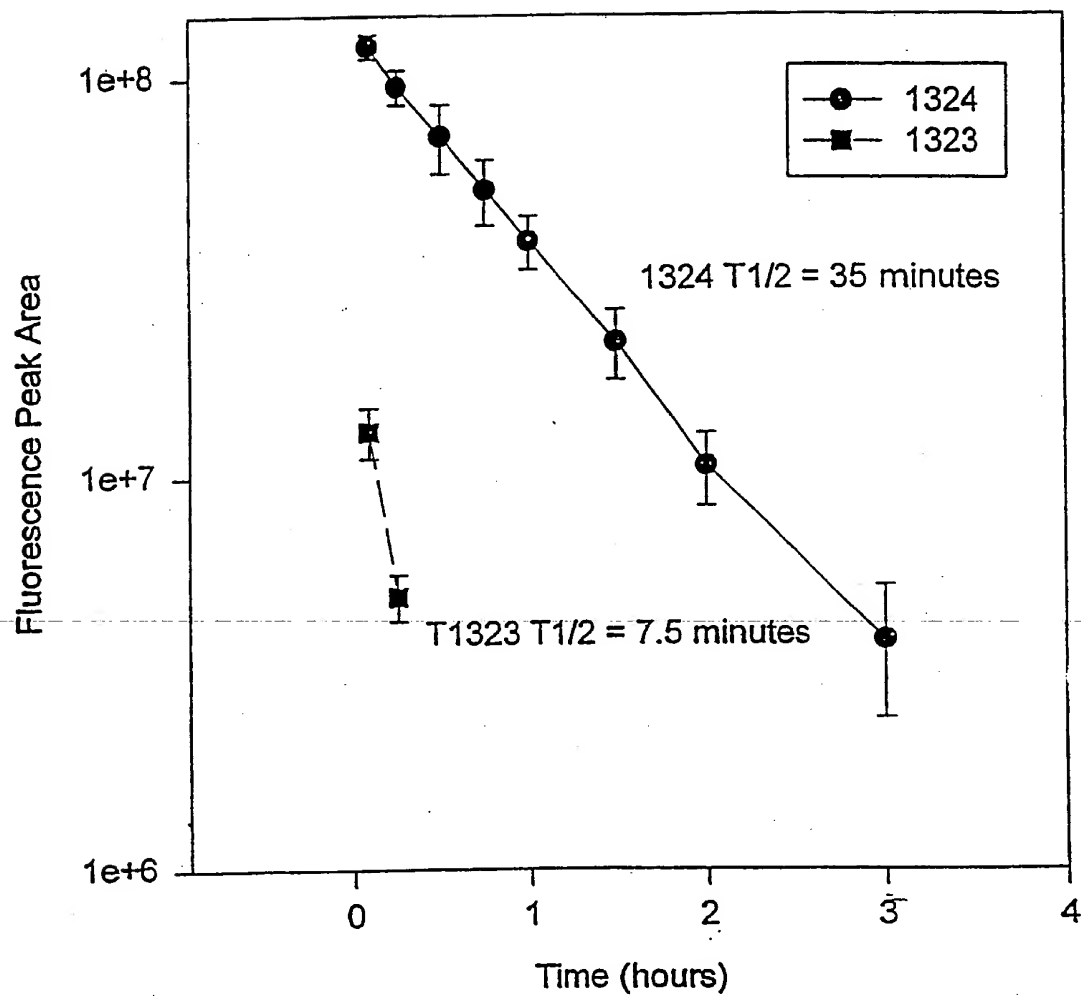


FIGURE 12A

16/27

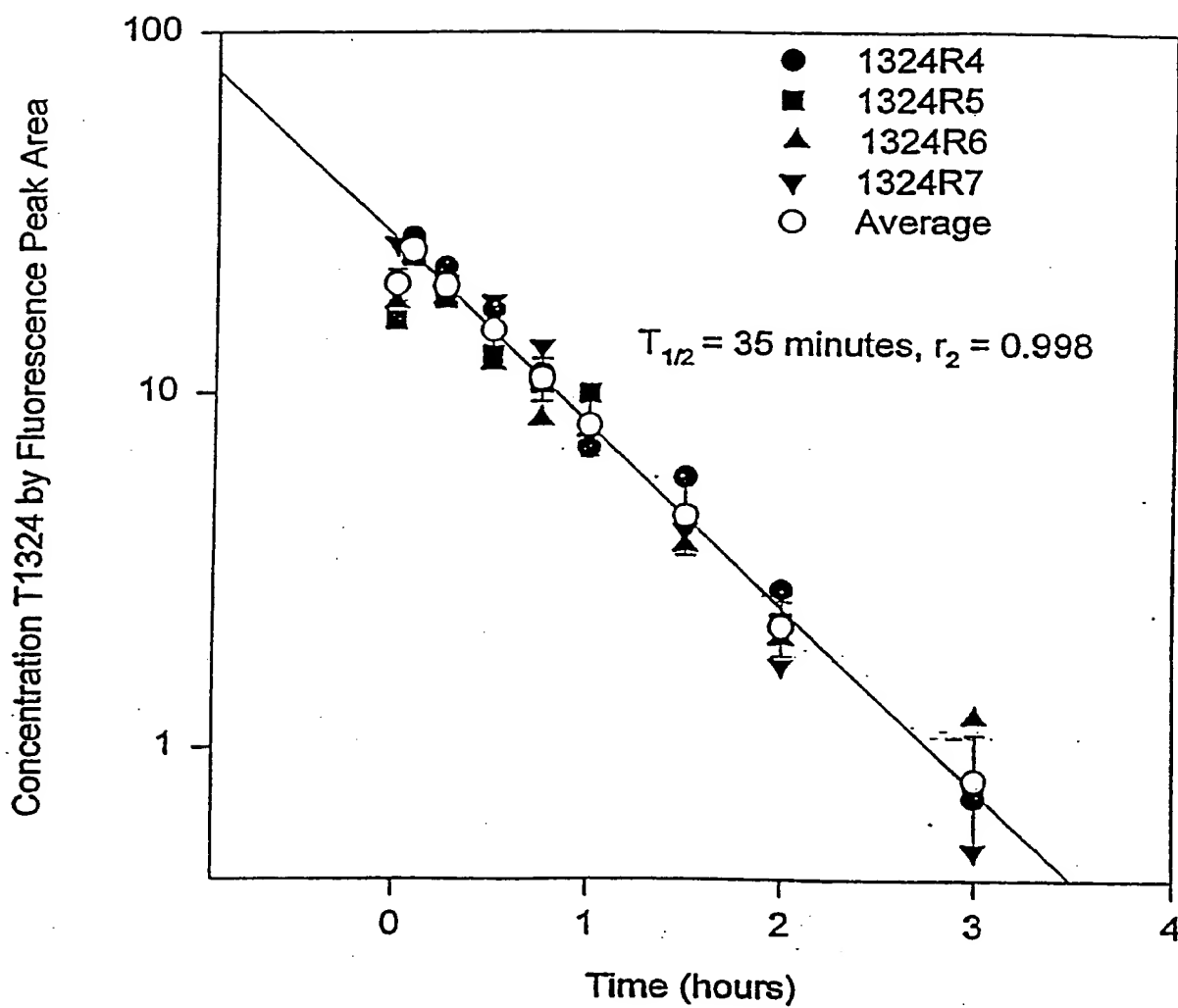


FIGURE 12B



[illegible]

FIGURE 13 cont'd.

19/27

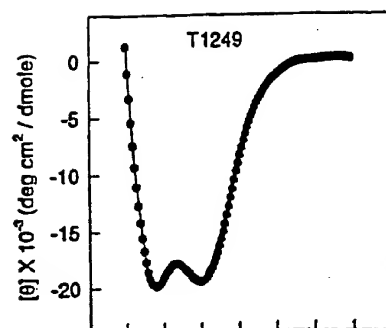


FIGURE 14A

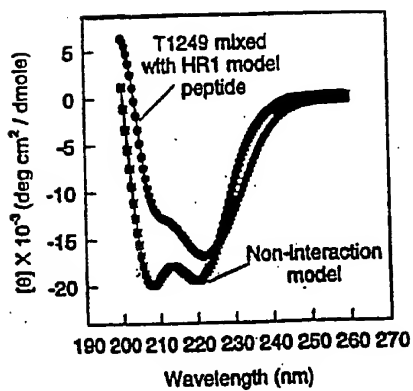


FIGURE 14B

20/27

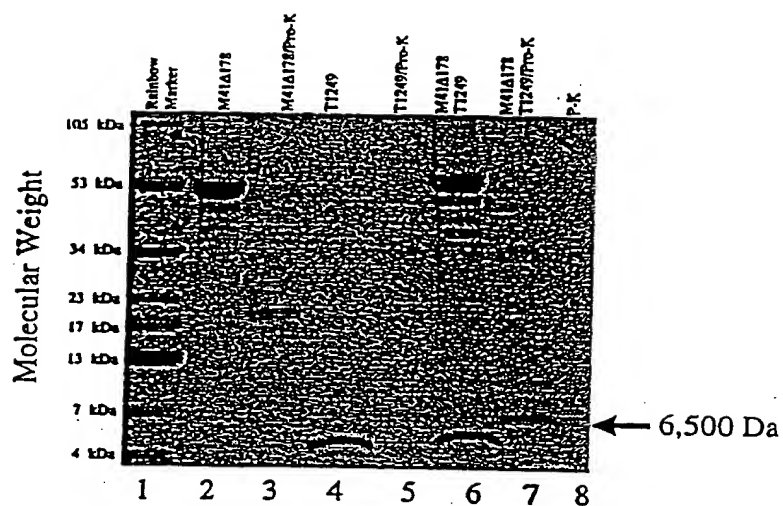


FIGURE 15

21/27

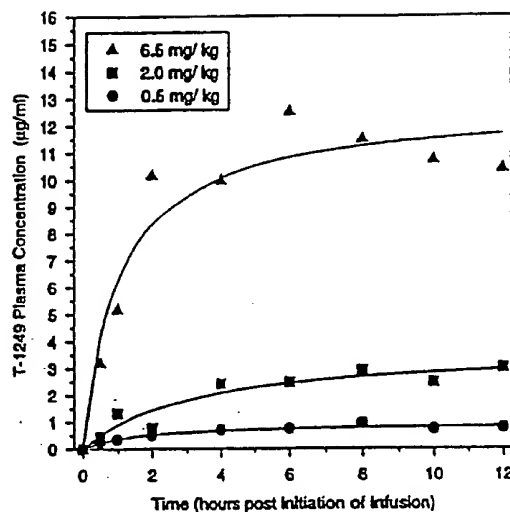


FIGURE 16 A

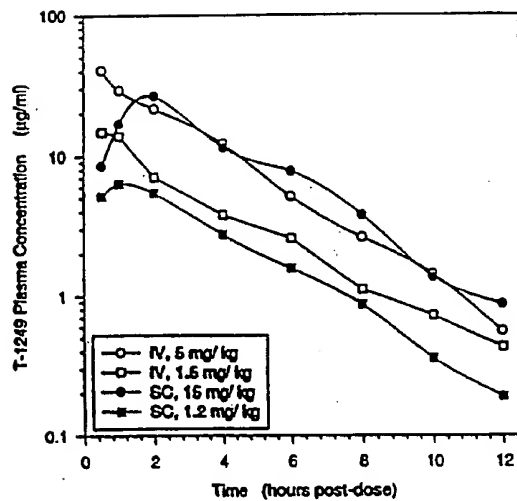


FIGURE 16 B

22/27

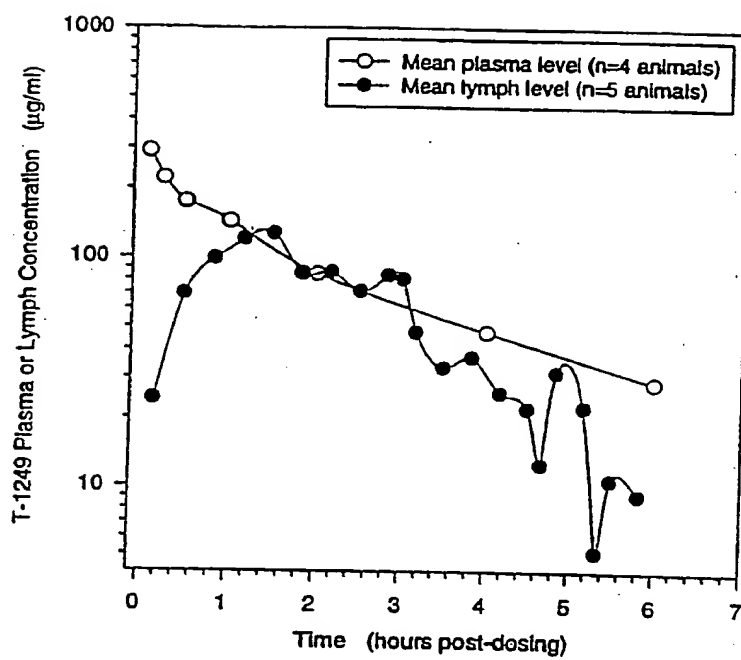


FIGURE 16C

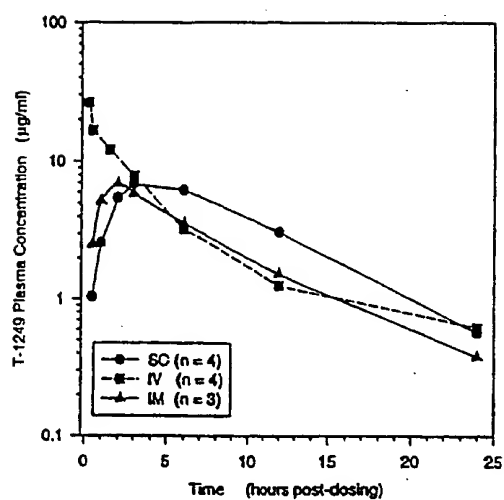


FIGURE 17A

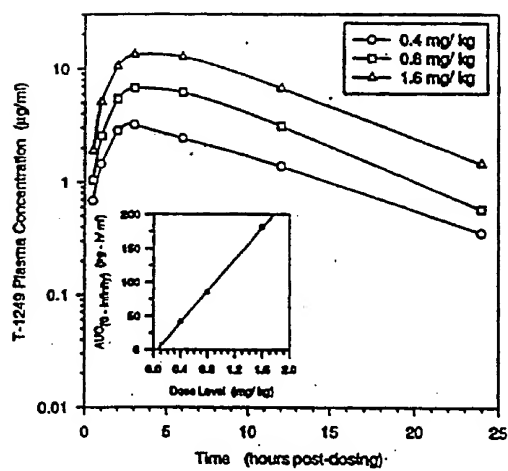


FIGURE 17B

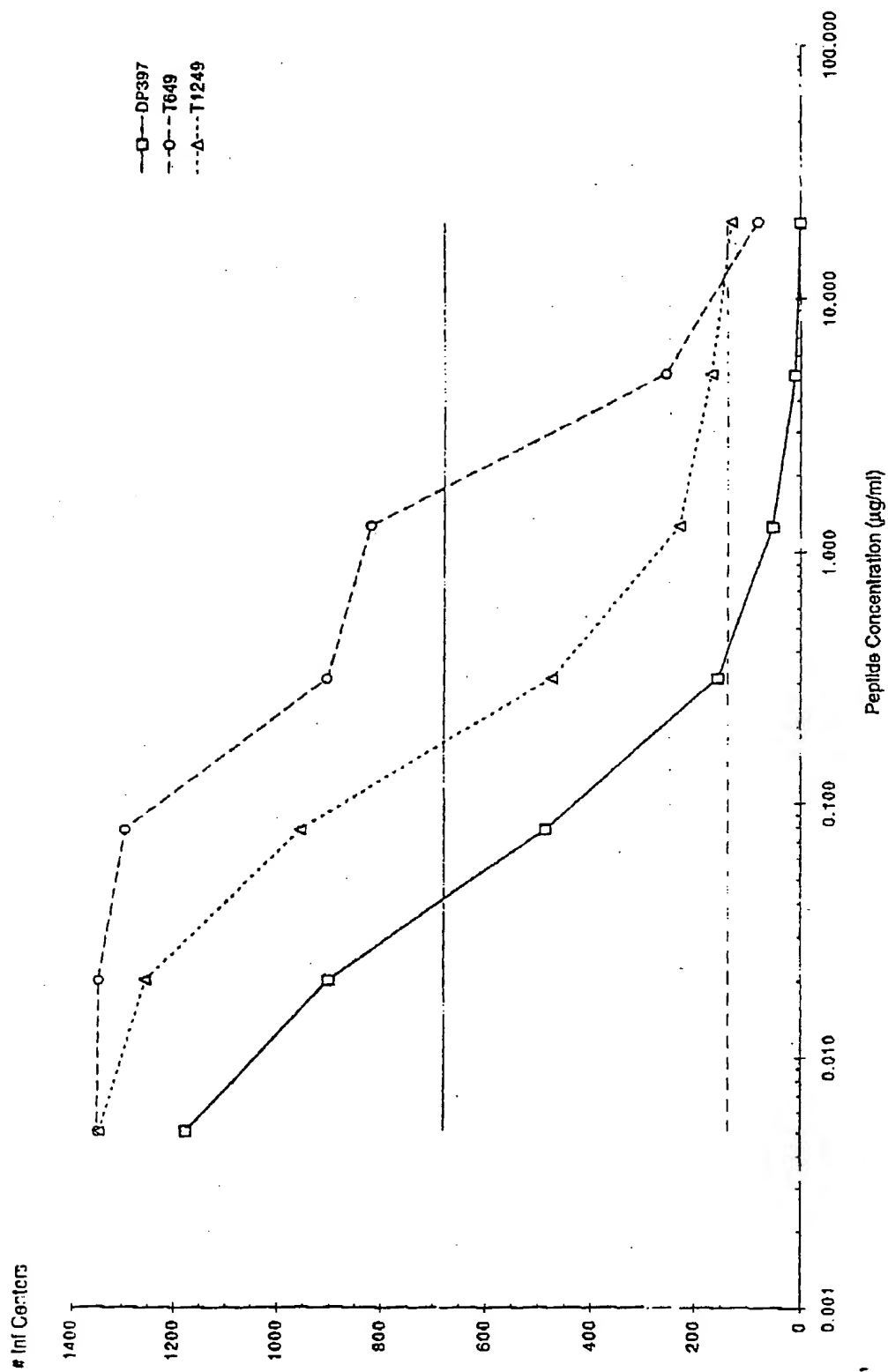


FIGURE 18A

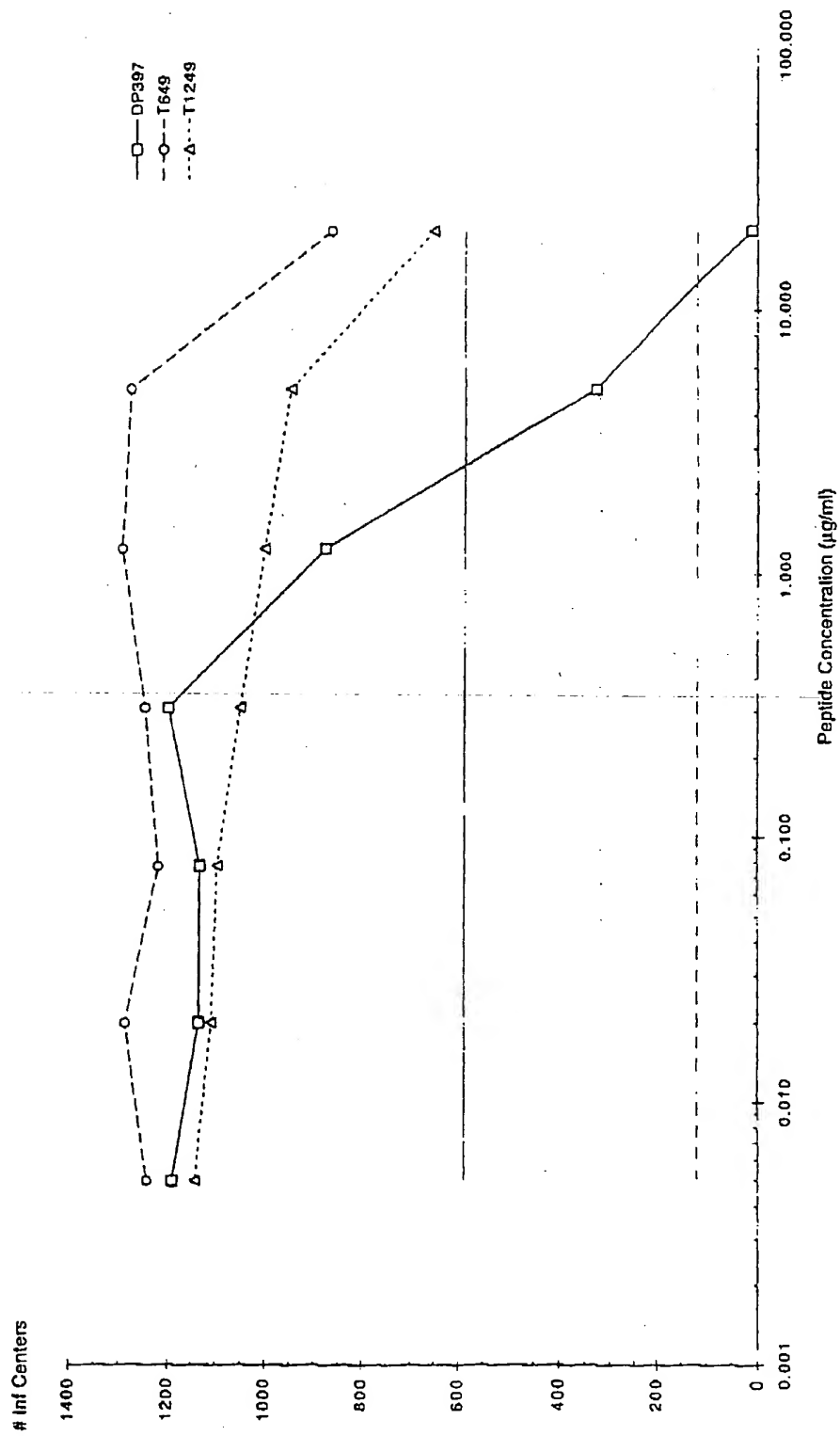


FIGURE 18B

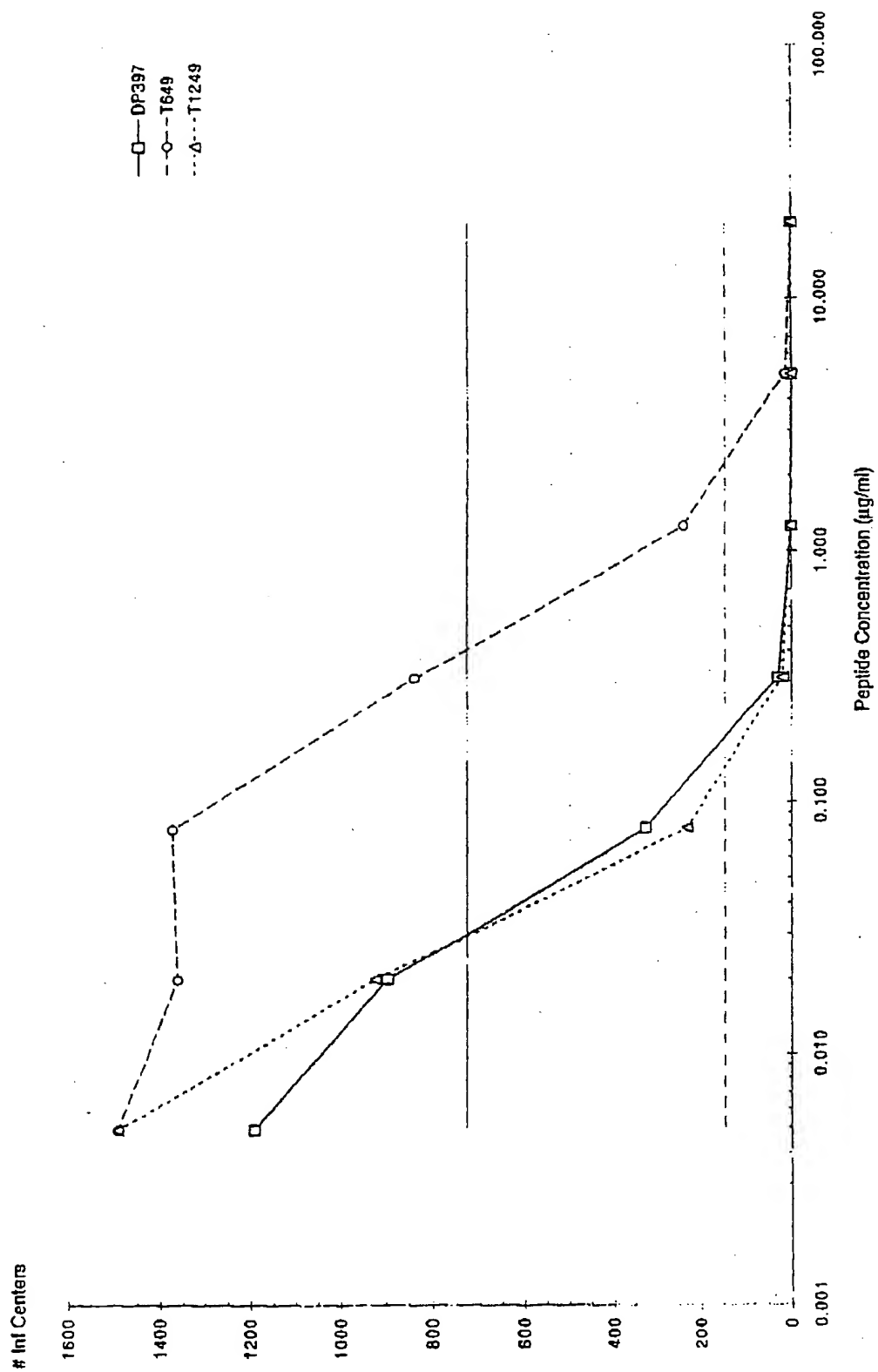


FIGURE 18C

27/27

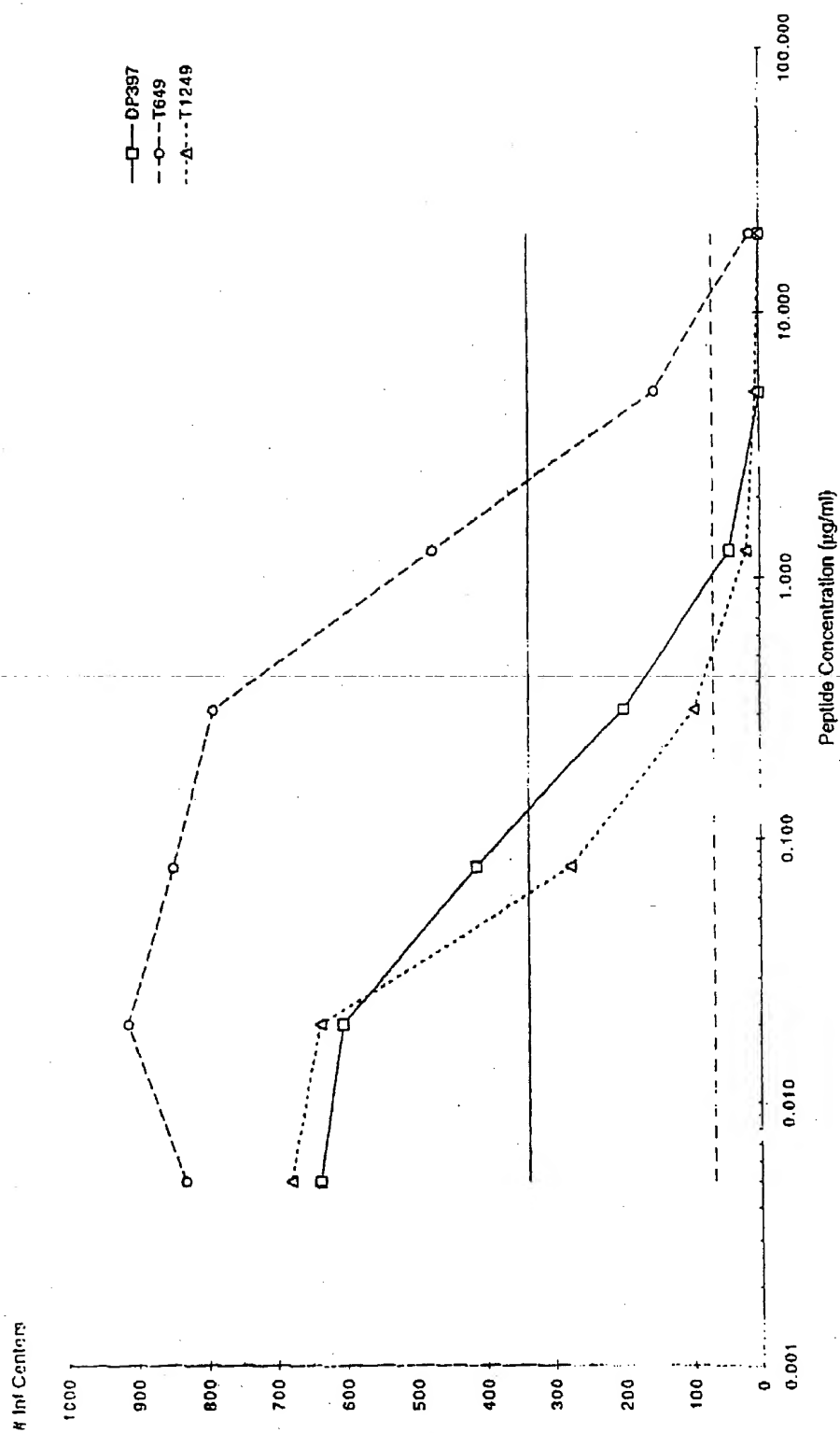


FIGURE 18D

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/18772

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/300, 313, 324, 326, 328, 350, 397, 398, 399; 514/2, 12, 13, 15

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, GENESEQ, SWISSPROT, PIR, STN

search terms: hybrid, chimeric, sequences of claims 9 and 16

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,723,129 A (POTTER ET AL) 03 March 1998 (03/03/98), abstract, column 4, lines 36-43, SEQ ID NO:8, especially residues 953-962.	1, 4, 7-10, 16, 18-20
X	US 5,763,160 A (C. WANG) 09 June 1998 (09/06/98), column 9, line 60 - column 10, line 39, column 15, line 25 - column 16, line 41, column 18, line 65 - column 19, line 10, column 20, lines 53-64.	1, 6-8, 18-20
X	US 5,843,913 A (LI ET AL) 01 December 1998 (01/12/98), Figure 2, SEQ ID NO:2, especially residues 506-533.	16
X	EP 0 272 858 A2 (REPLIGEN CORPORATION) 29 June 1988 (29/06/88), page 9, line 54 - page 10, line 23, page 17, line 1, page 18, lines 11-15, Table 3.	1, 2, 4-12, 16, 18-20

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

08 AUGUST 2000

Date of mailing of the international search report

23 AUG 2000

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JEFFREY E. RUSSEL

Telephone No. (703) 308-0196

## INTERNATIONAL SEARCH REPORT

 International application No.  
 PCT/US00/18772

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 578 293 A1 (AKZO N.V.) 12 January 1994 (12/01/94), page 3, lines 35-58, page 4, lines 45-49.	1, 2, 4-12, 16, 18-20
X	WO 91/07664 A1 (CAMBRIDGE BIOSCIENCE CORPORATION) 30 May 1991 (30/05/91), page 4, lines 17-26, page 10, lines 9-17, Examples 3 and 4, Figures 4, 8, 12, 15, and 21.	1, 2, 4, 6-8, 18-20
X, P	US 5,968,776 A (KLEIN ET AL) 19 October 1999 (19/10/99), abstract, Figures 1 and 5.	1, 4, 7-10, 16, 18-20
X --- Y	US 5,464,933 A (BOLOGNESI ET AL) 07 November 1995 (07/11/95), column 6, lines 18, 20, 21, 24-30, SEQ ID NOS:1 and 6, claim 1.	1, 2, 6-9, 12, 16, 18-20 --- 17
Y	US 5,358,934 A (BOROVSKY ET AL) 25 October 1994 (25/10/94), column 2, line 64 - column 3, line 2.	17
X	US 5,357,041 A (ROBERTS ET AL) 18 October 1994 (18/10/94), Table 2, column 14, lines 53-55.	1, 2, 4, 7, 8, 18-20
X,P	WO 99/59615 A1 (TRIMERIS, INC.) 25 November 1999 (25/11/99), see entire document, especially claims 1-20.	1-20

Form PCT/ISA/210 (continuation of second sheet) (July 1998)\*

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/18772

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

A61K 38/02, 38/08, 38/10, 38/16, 38/18, 38/19, 38/22; C07K 7/06, 7/08, 14/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

530/300, 313, 324, 326, 328, 350, 397, 398, 399; 514/2, 12, 13, 15





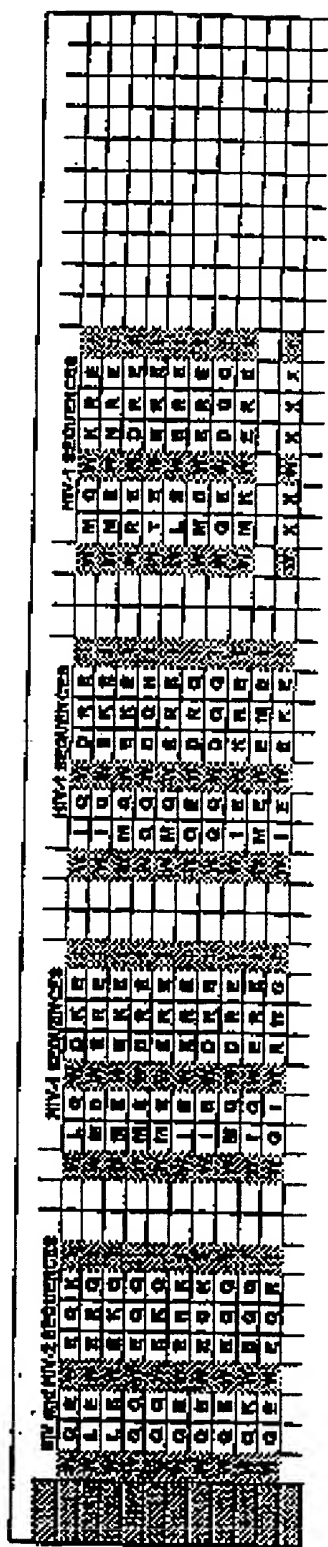


Figure 2A

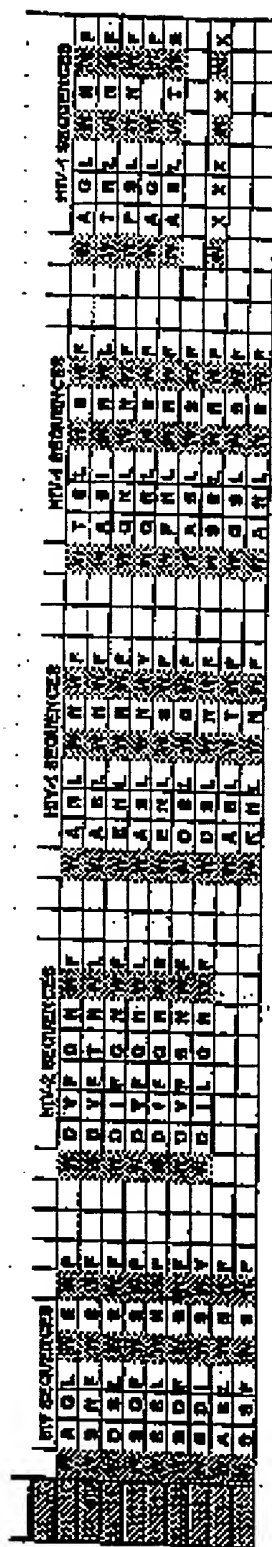


Figure 2B

3/27

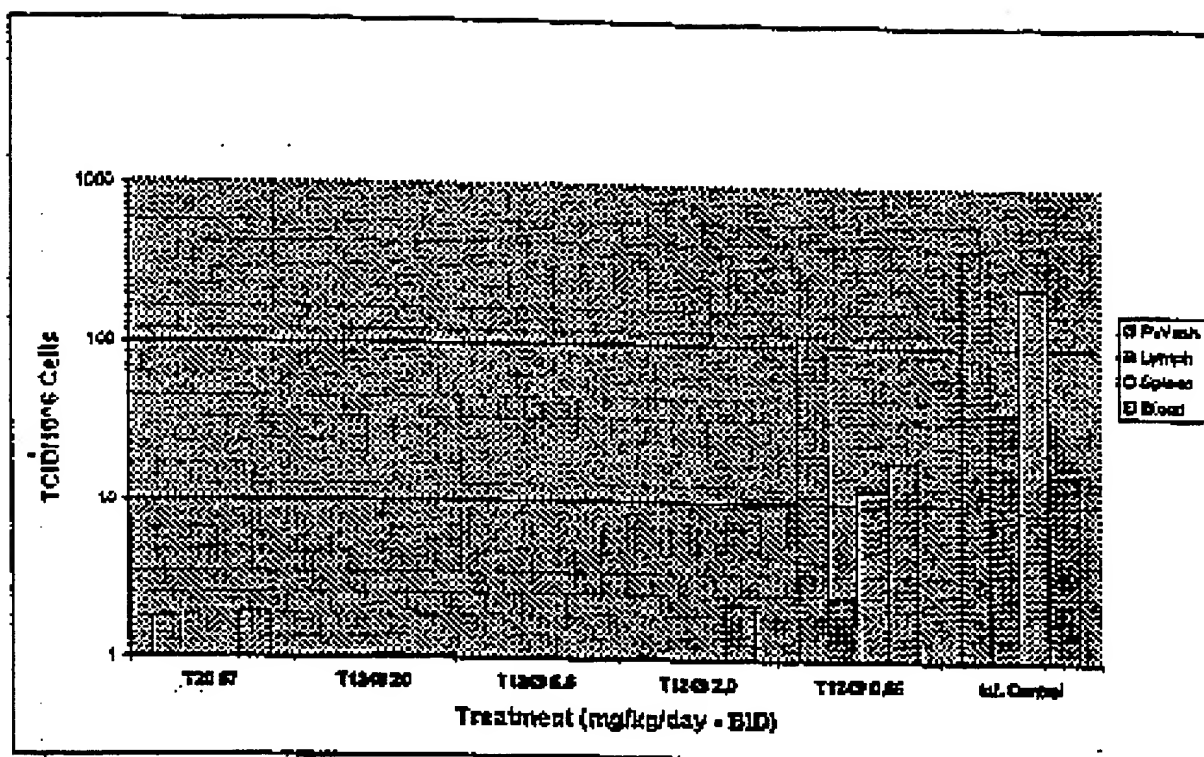


FIGURE 3

4/27

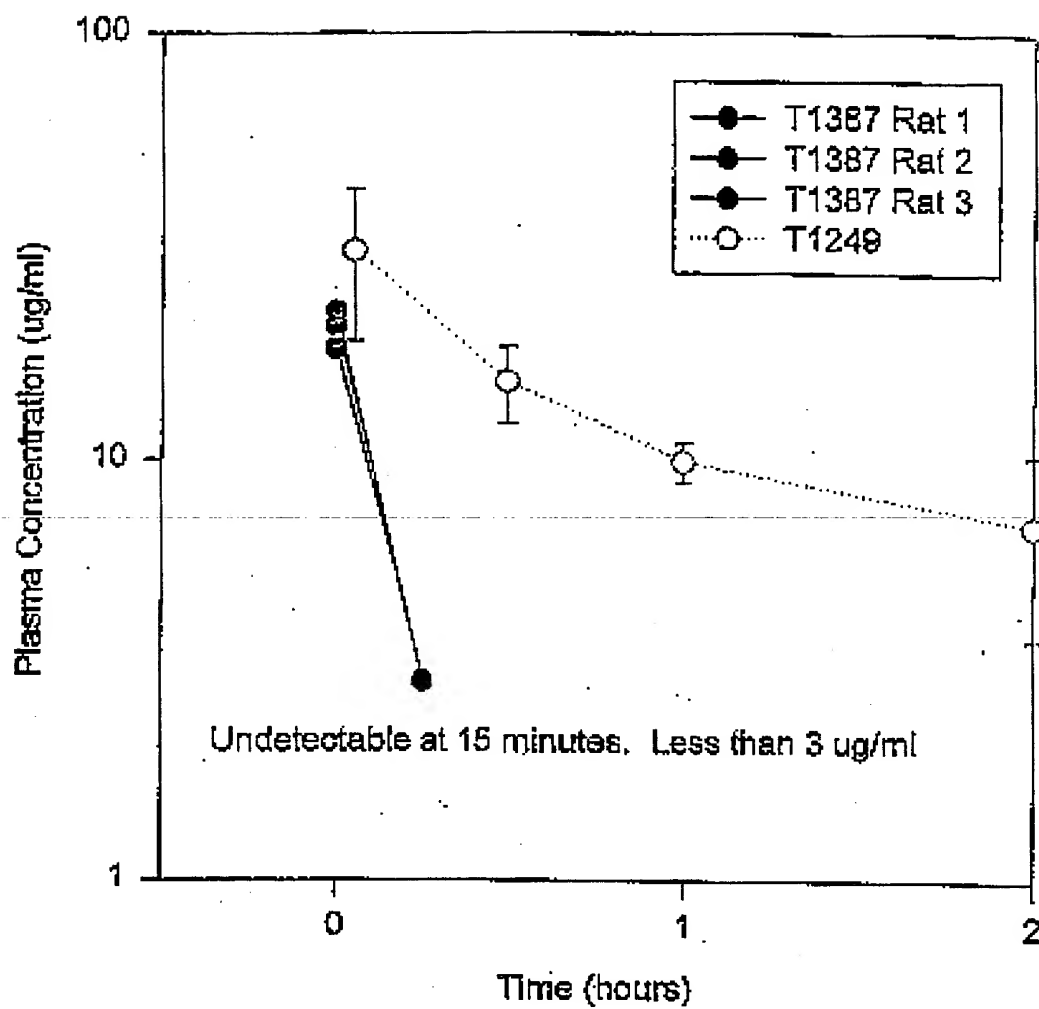


FIGURE 4A

5/27

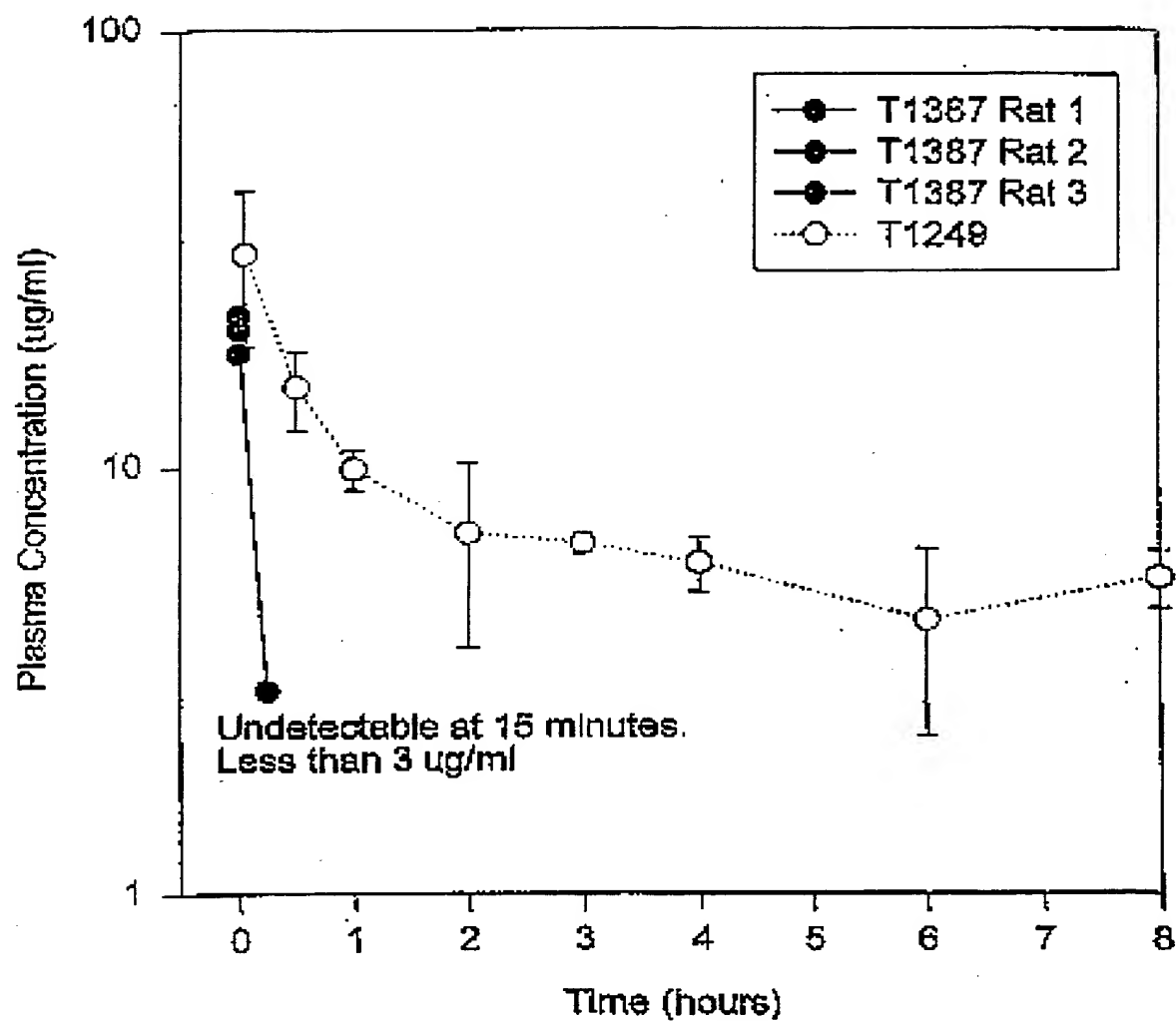
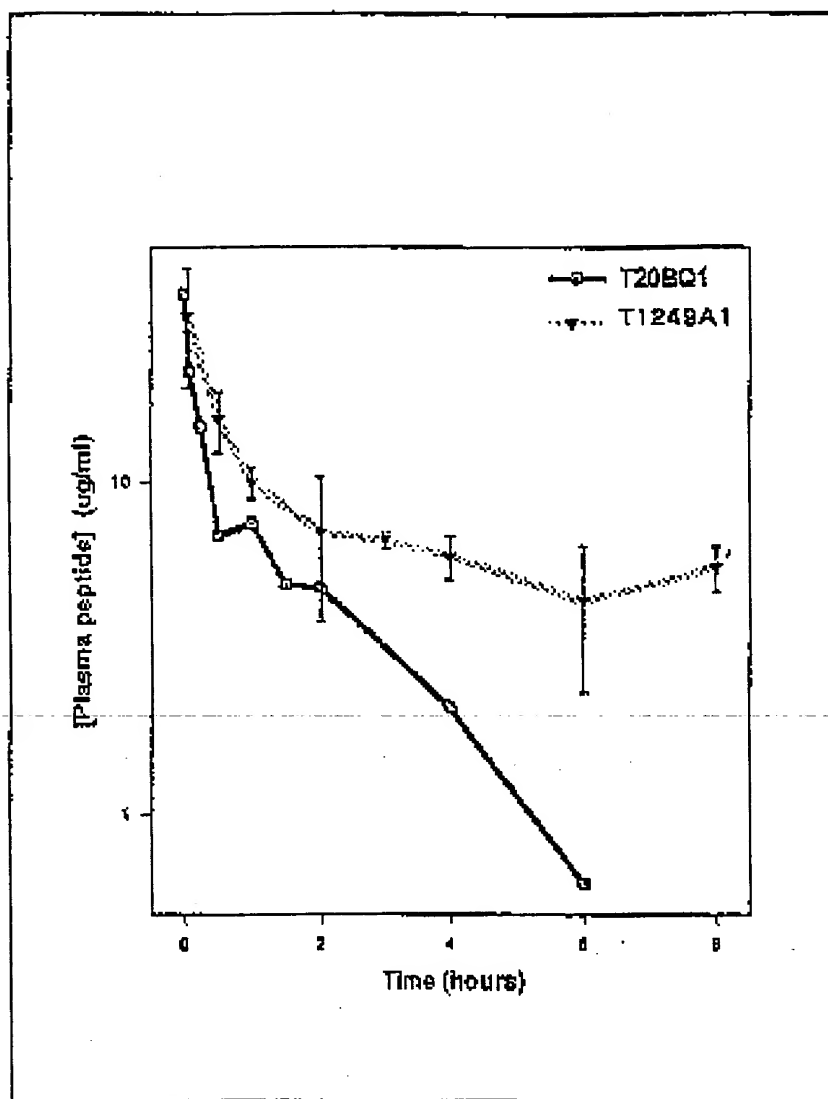


FIGURE 4B



Pharmacokinetic Parameters		T20BQ1	T1248A1
Dose (mg/kg IV)		2.5	2.5
Detection method		Fluorescence	Fluorescence
		HPLC	HPLC
$T_{1/2\alpha}$ (h)		1.6	4.71
$CL_r$ (ml/h)		27.94	9.62
$AUC_{0-8}$ (ug (h/ml))		26.12	71.43

FIGURE 5

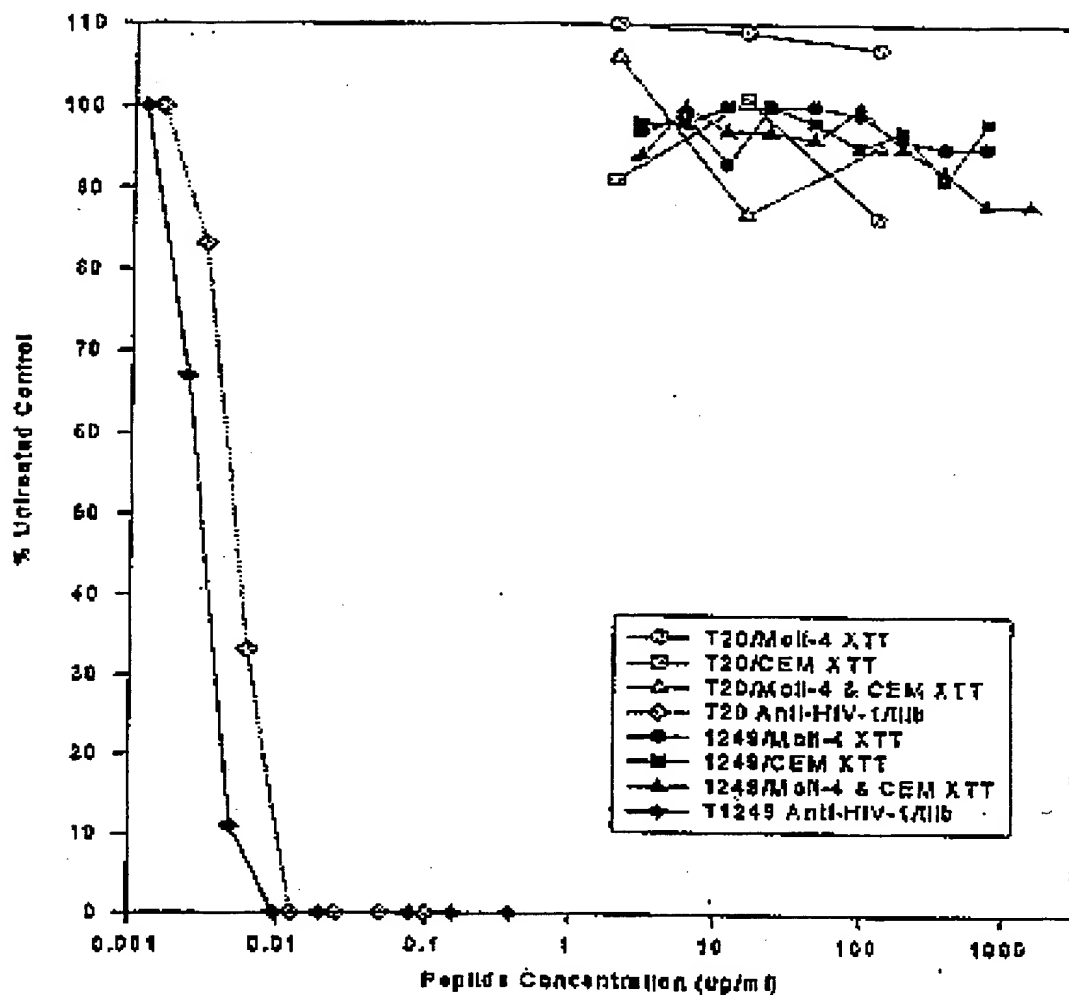


FIGURE 6

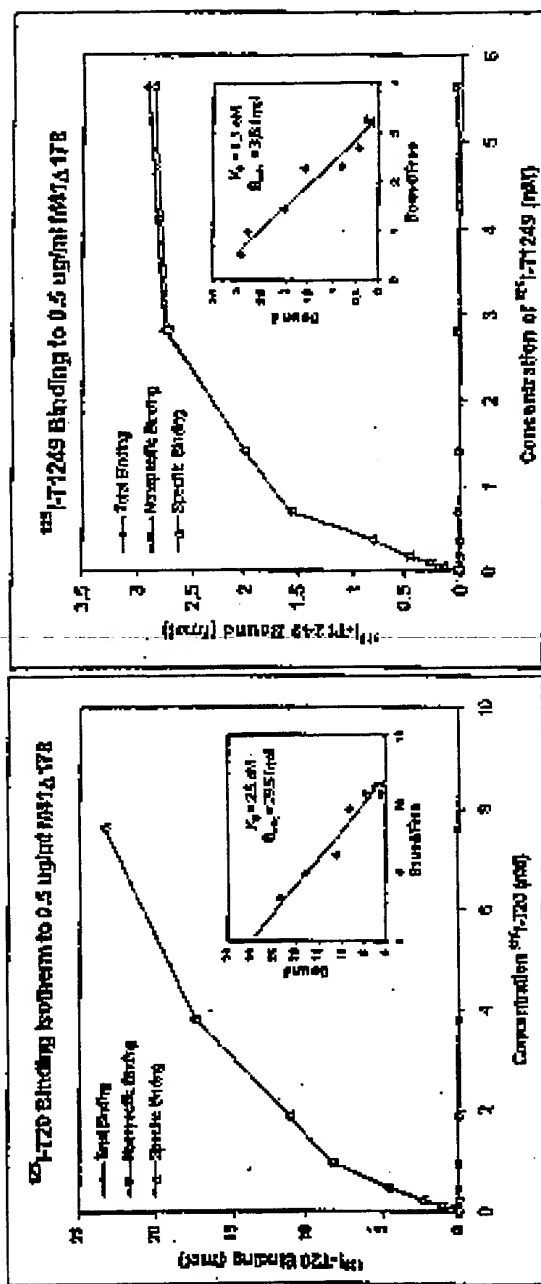


FIGURE 7

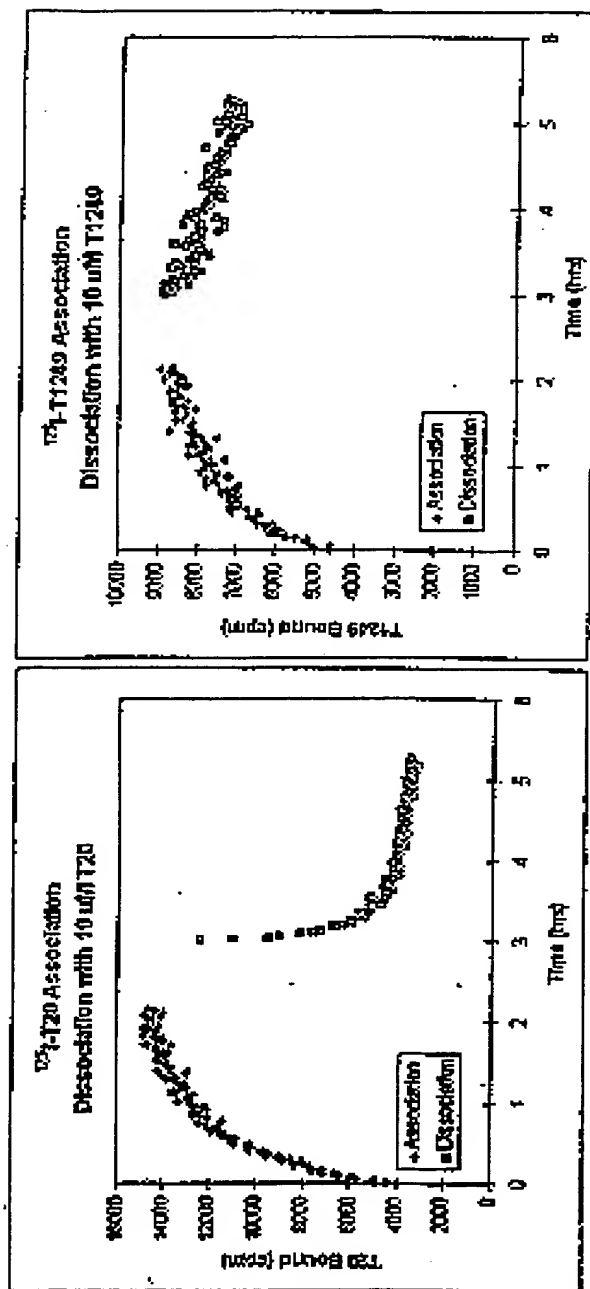


Figure 8

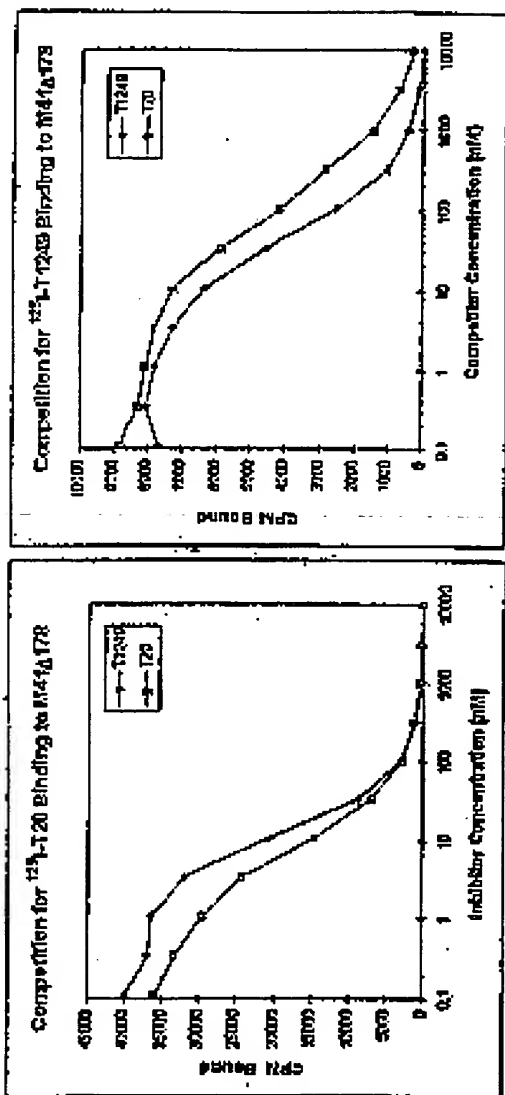


Figure 9

11/27

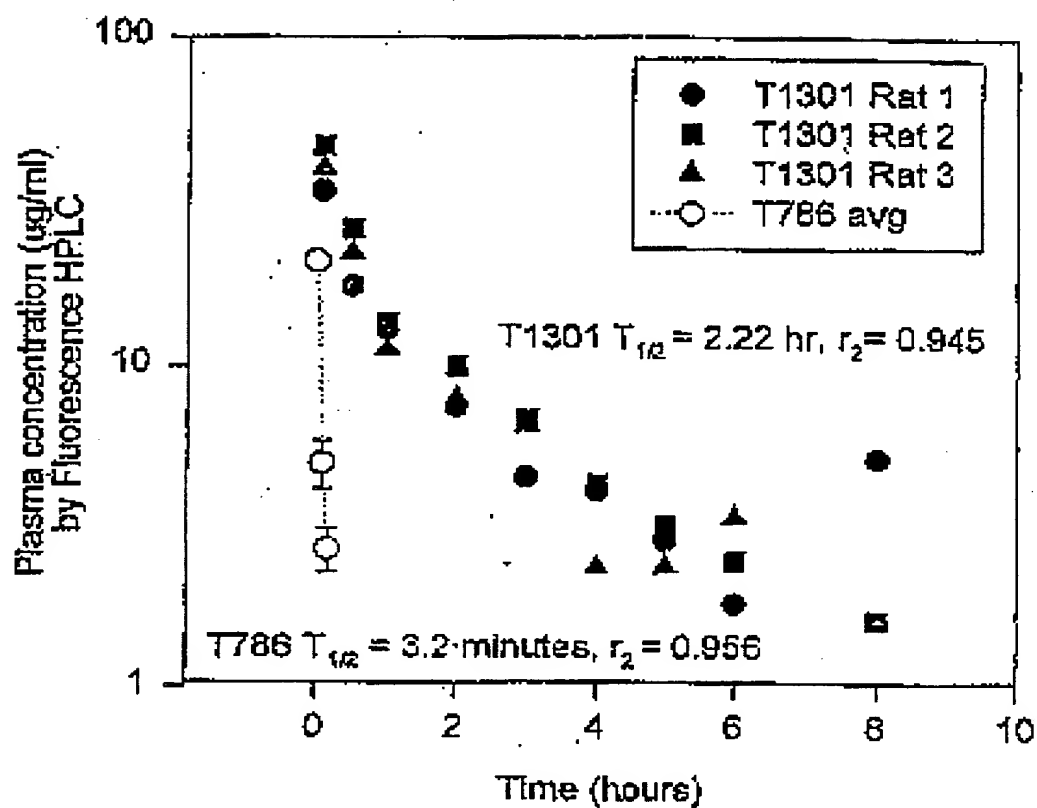


FIGURE 10A

12/27

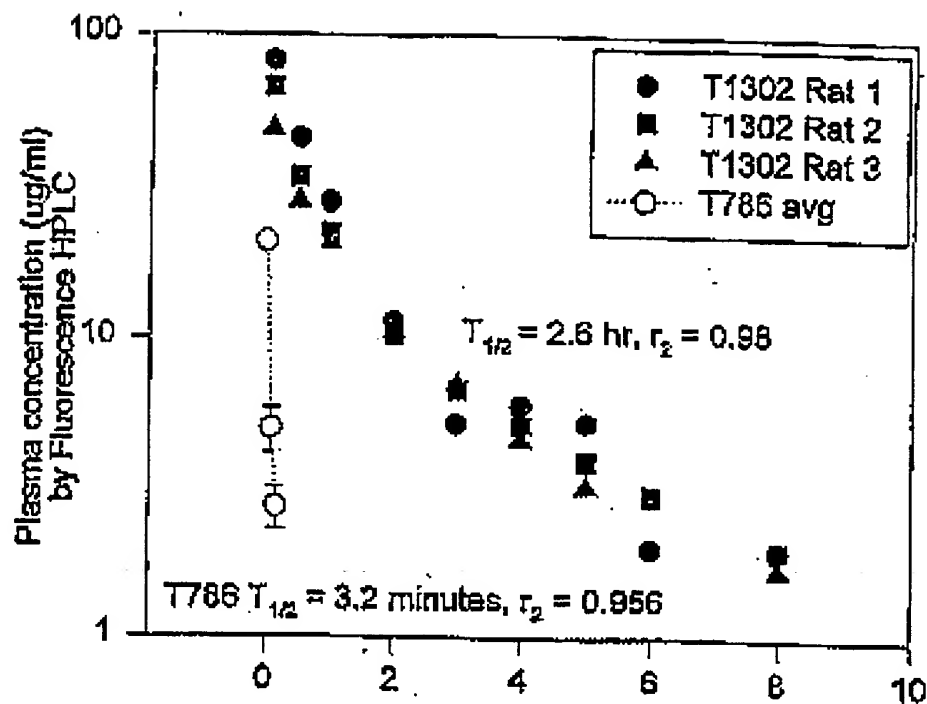


FIGURE 10B

Virus RSV

Concentration (mg/ml)

2	3	4	5	6	7	8	9	10	11	12	13	14
60.000	20.000	12.500	6.250	3.125	1.563	0.781	0.391	0.196	0.098	0.049	0.025	0.012

1130241	1130242	1130243	1130244	1130245	1130246	1130247	1130248	1130249	1130250	1130251	1130252	1130253
3	4	7	12	21	39	61	91	121	151	181	211	241

% Infection

1130241	1130242	1130243	1130244	1130245	1130246	1130247	1130248	1130249	1130250	1130251	1130252	1130253
0.03	0.04	0.06	0.10	0.16	0.25	0.39	0.59	0.89	1.19	1.49	1.79	2.09

Fluorescence Assay

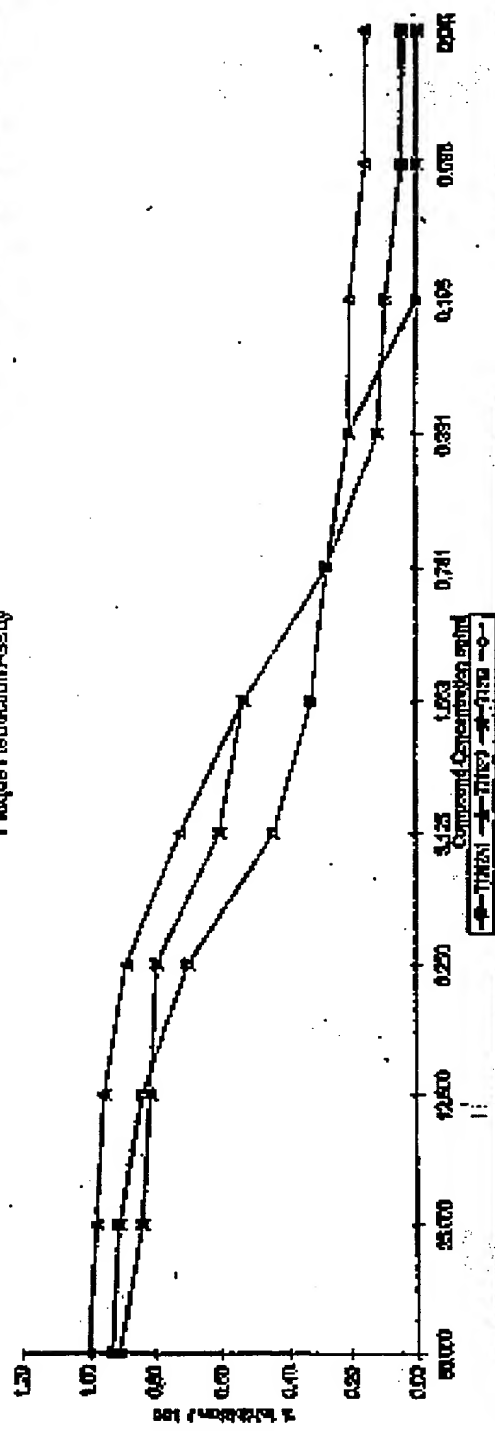


FIGURE 11A

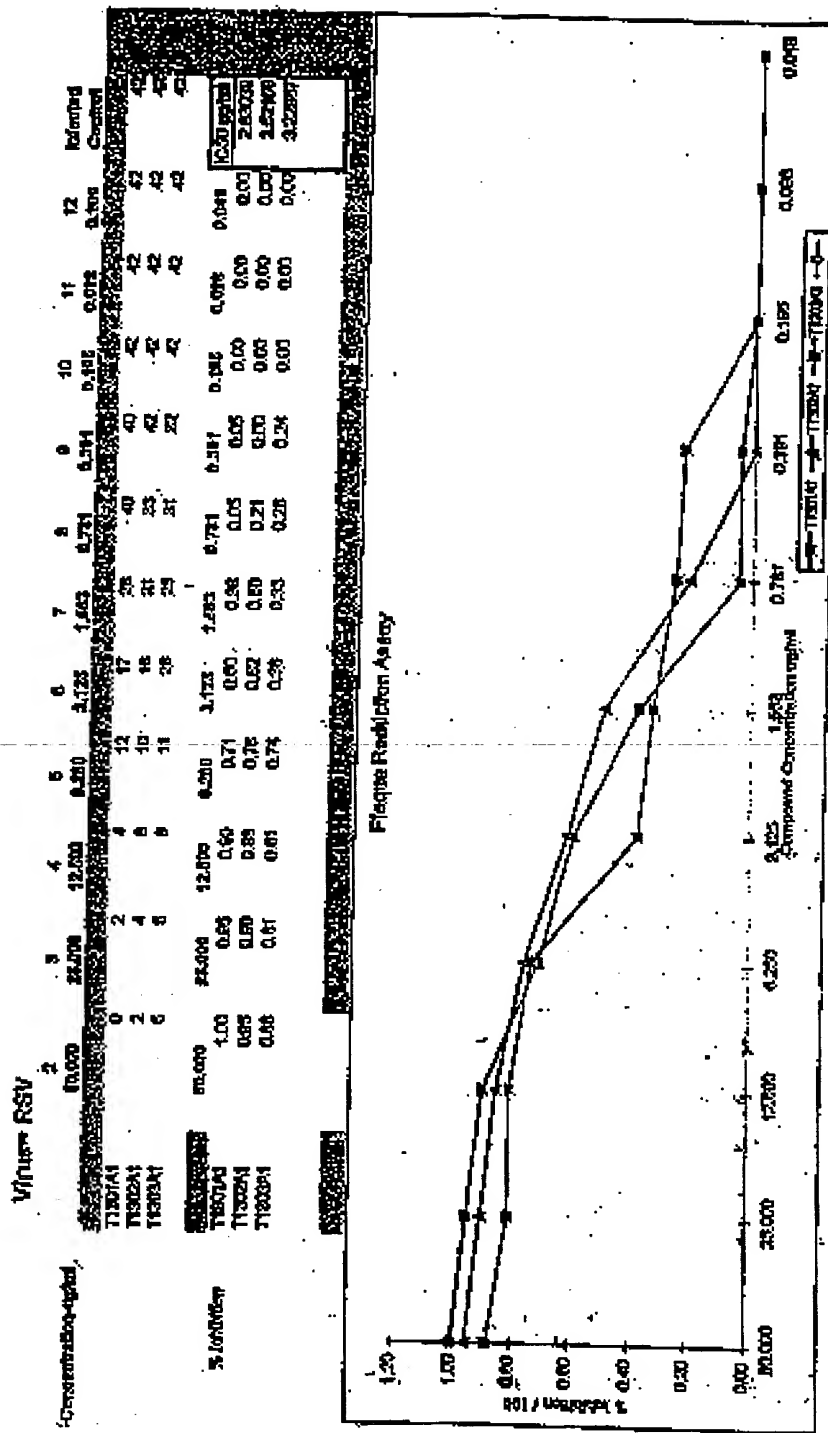


Figure 11 B

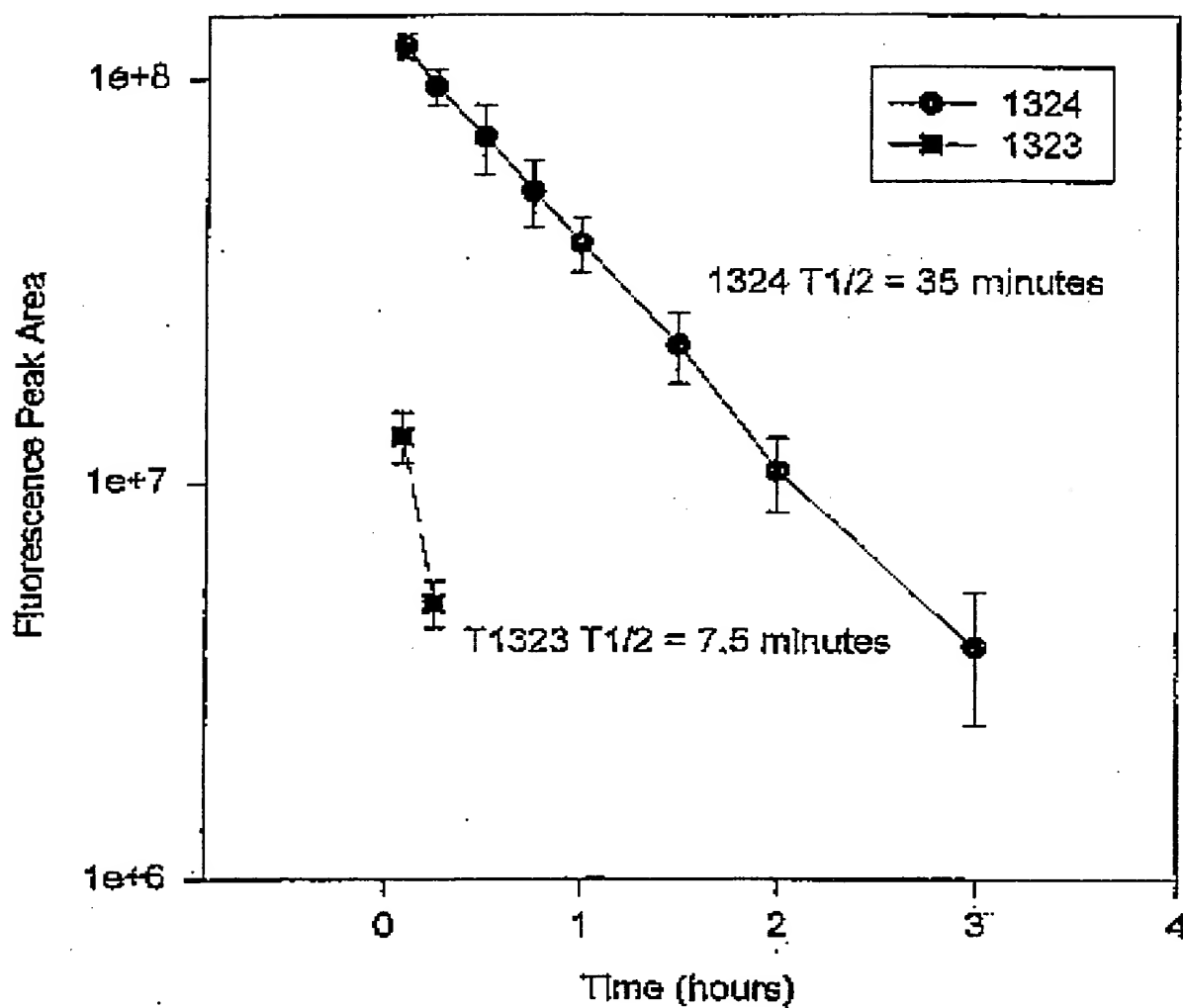


FIGURE 12A

16/27

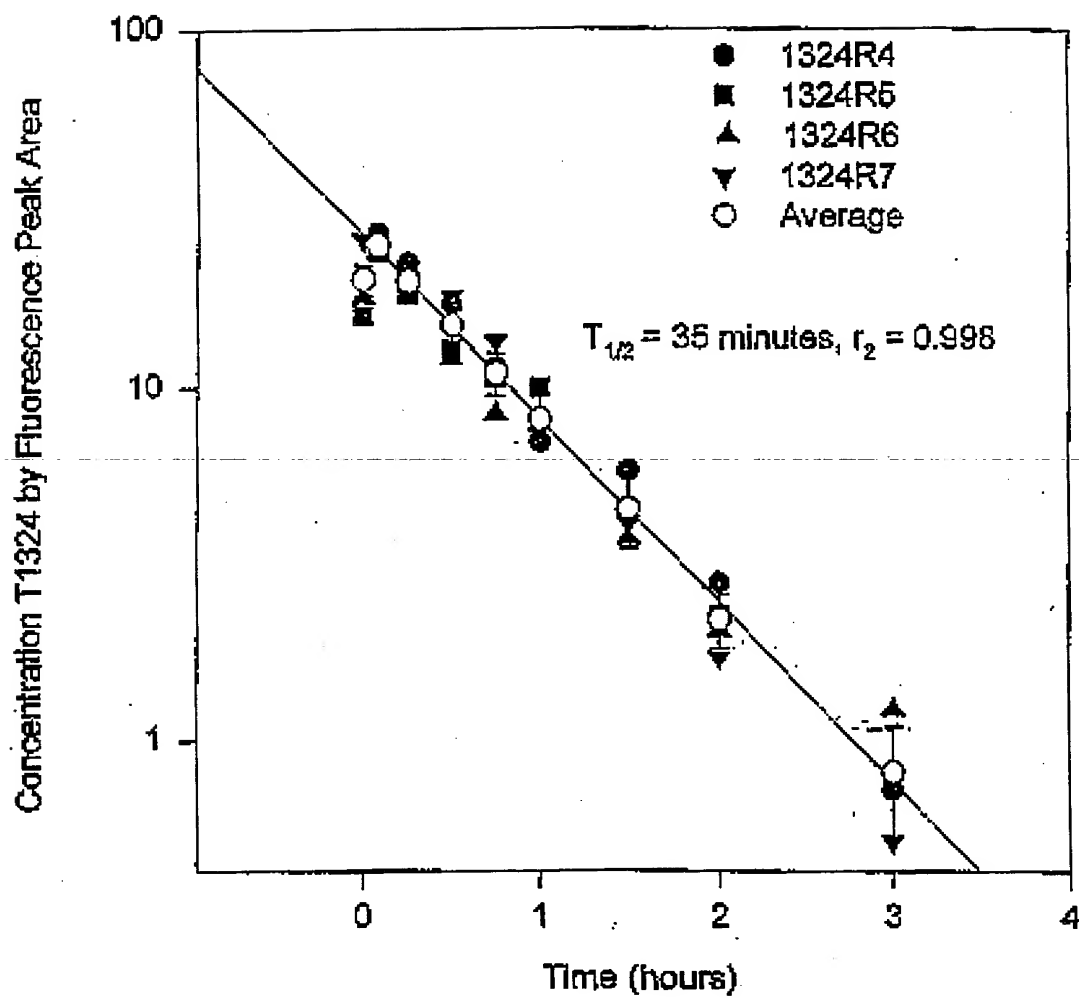


FIGURE 12B

17/27

[illegible]

FIGURE 13



19/27

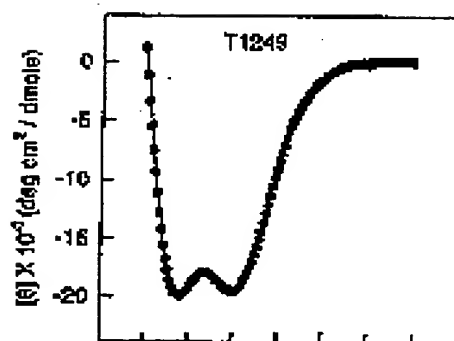


FIGURE 14A

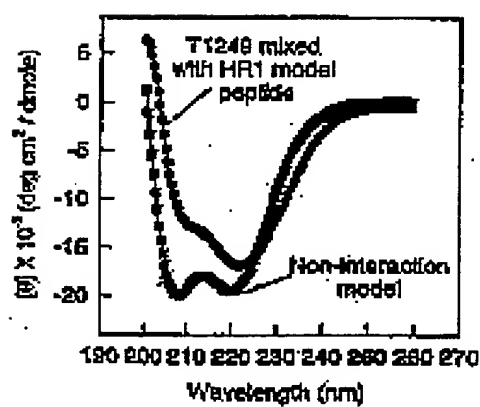


FIGURE 14B

20/27

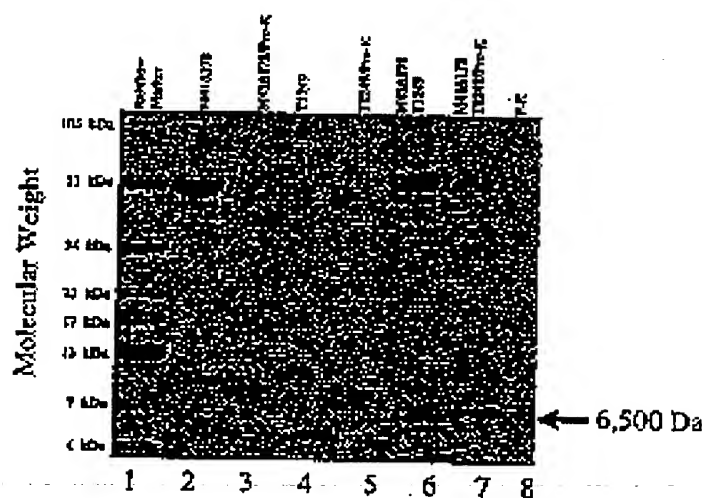


FIGURE 15

21/27

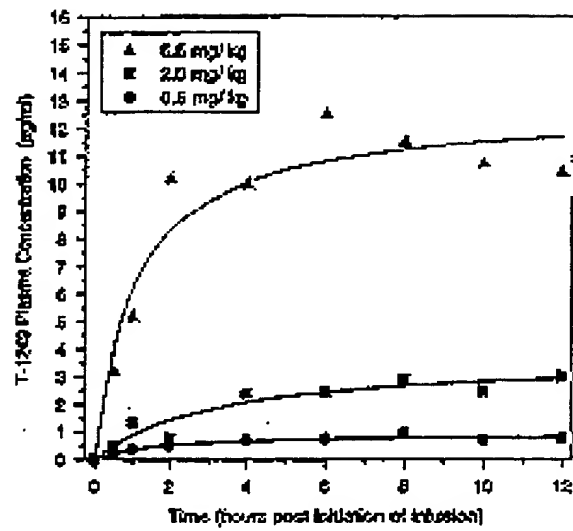


FIGURE 16A

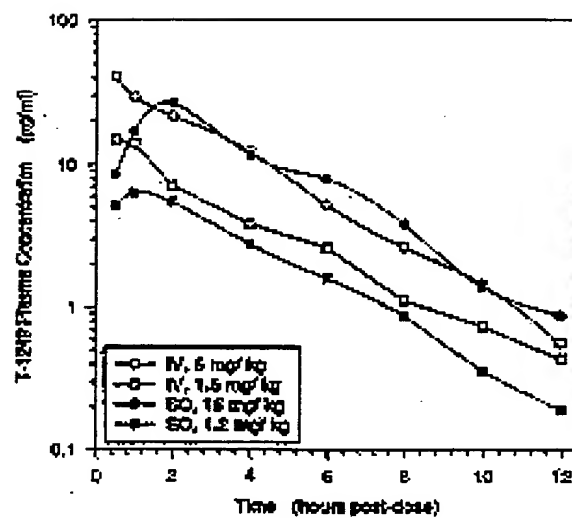


FIGURE 16B

22/27

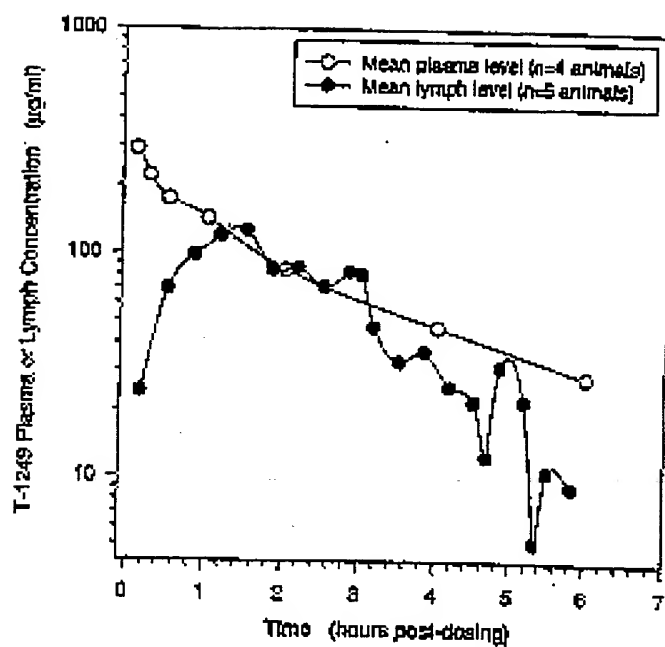


FIGURE 16C

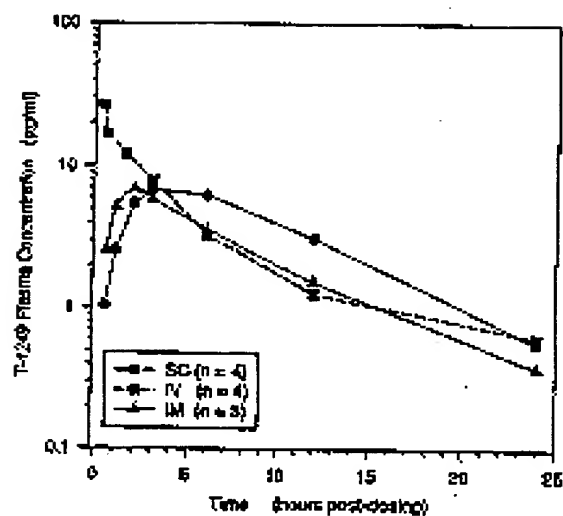


FIGURE 17A

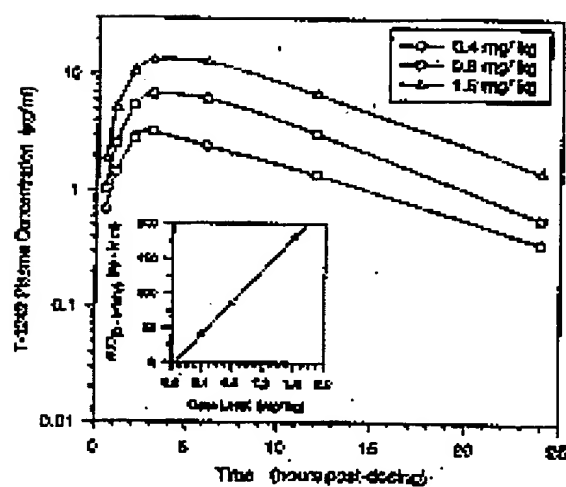


FIGURE 17B

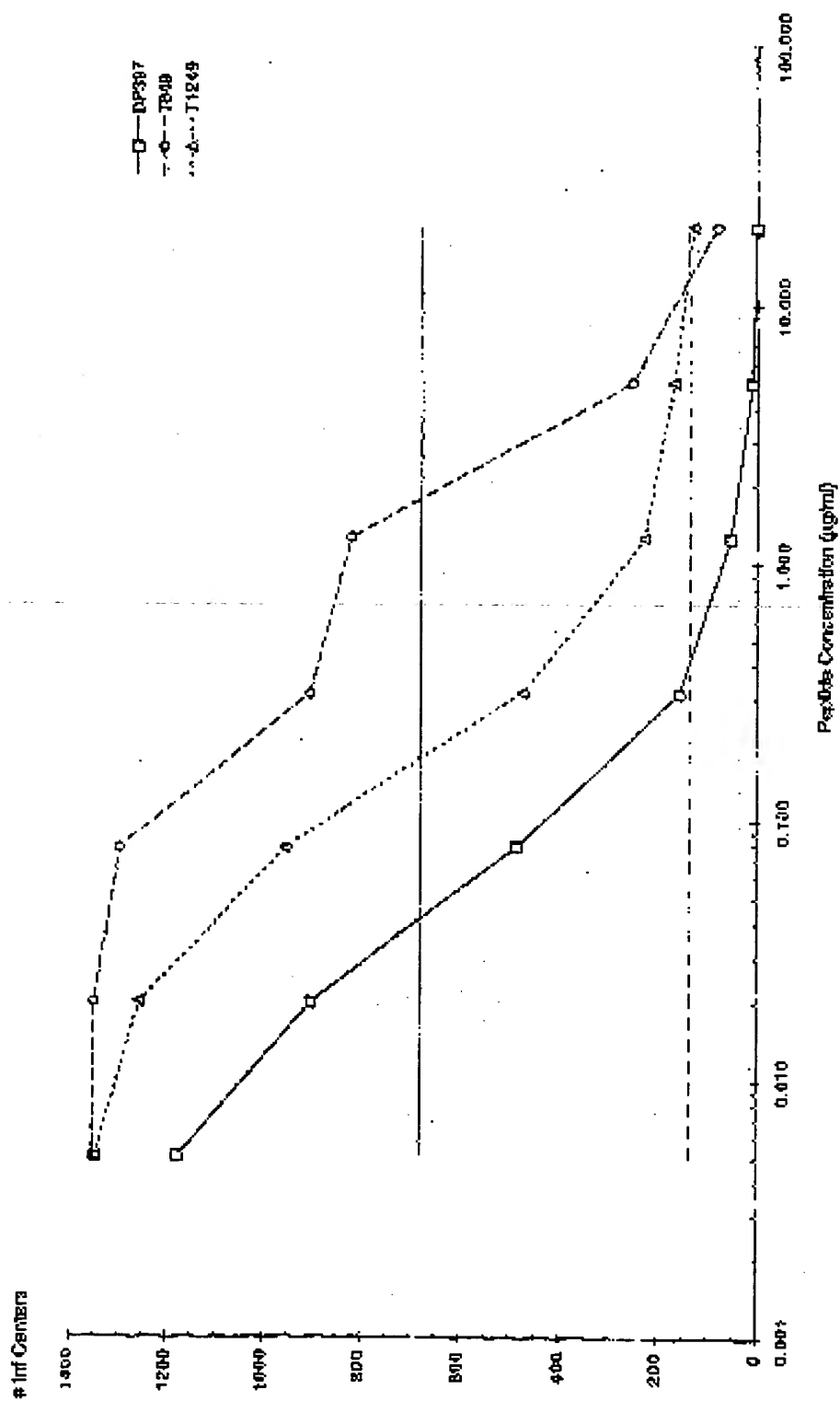


FIGURE 18A

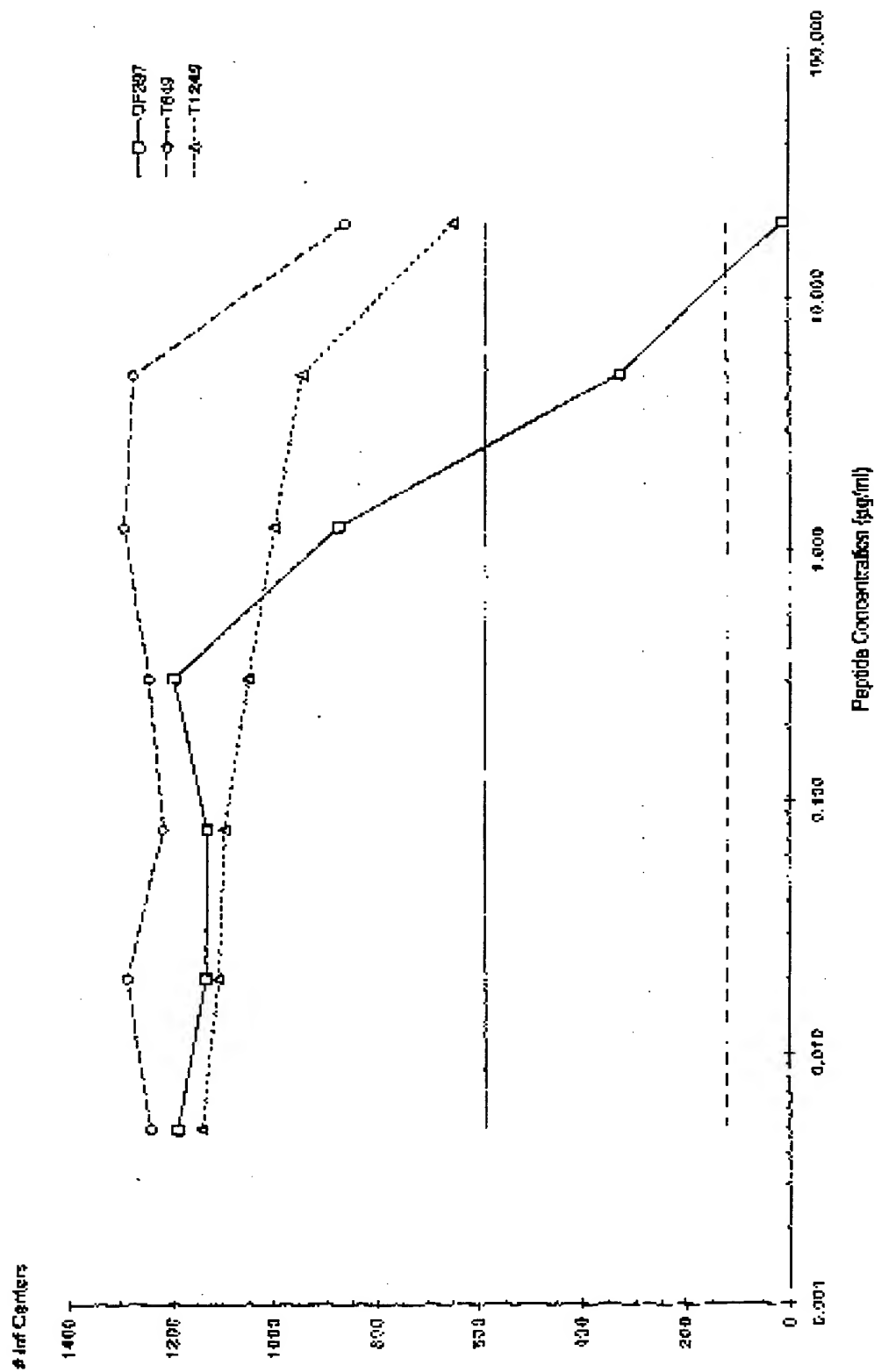


FIGURE 18B

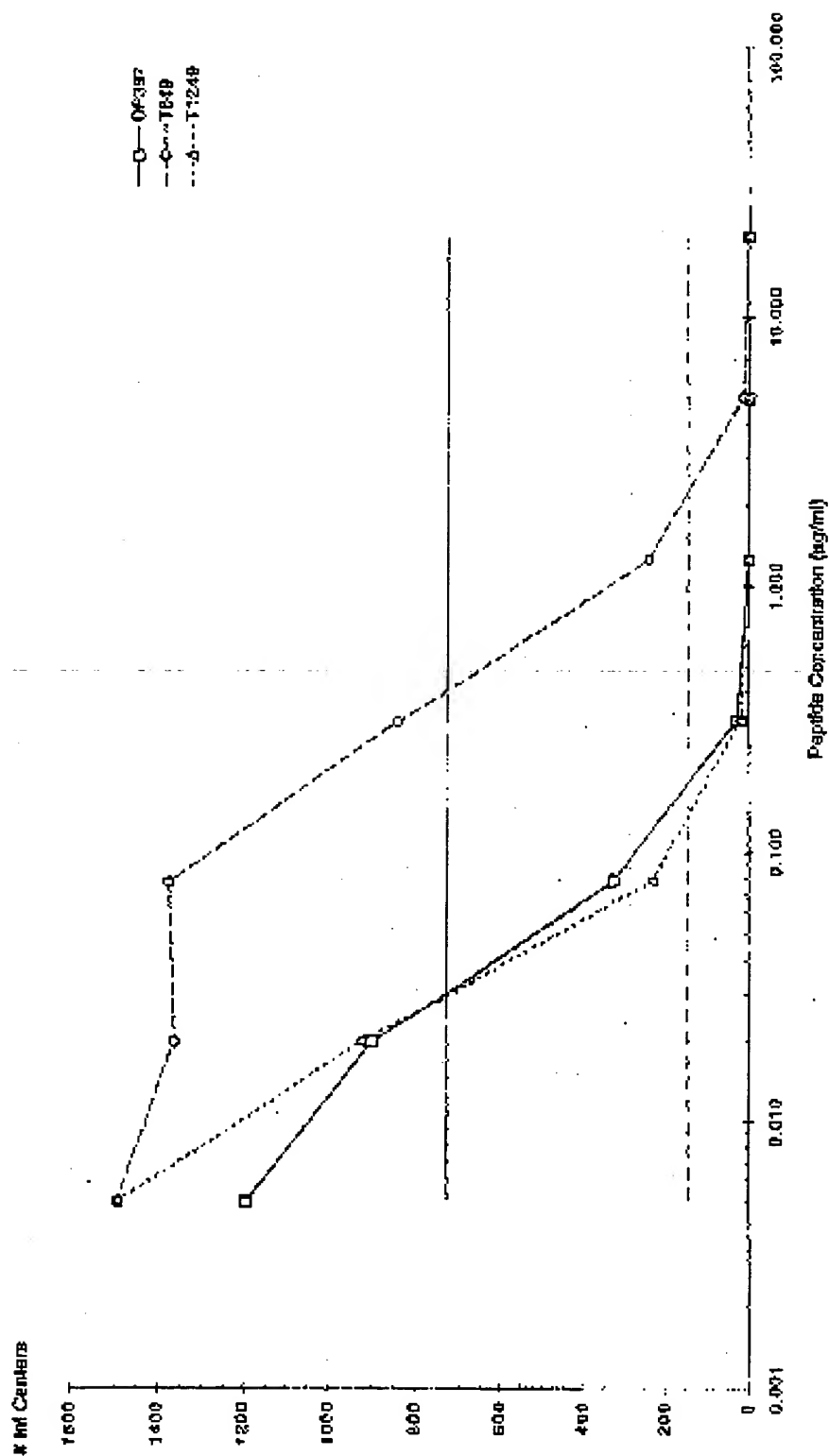


FIGURE 18C

27/27

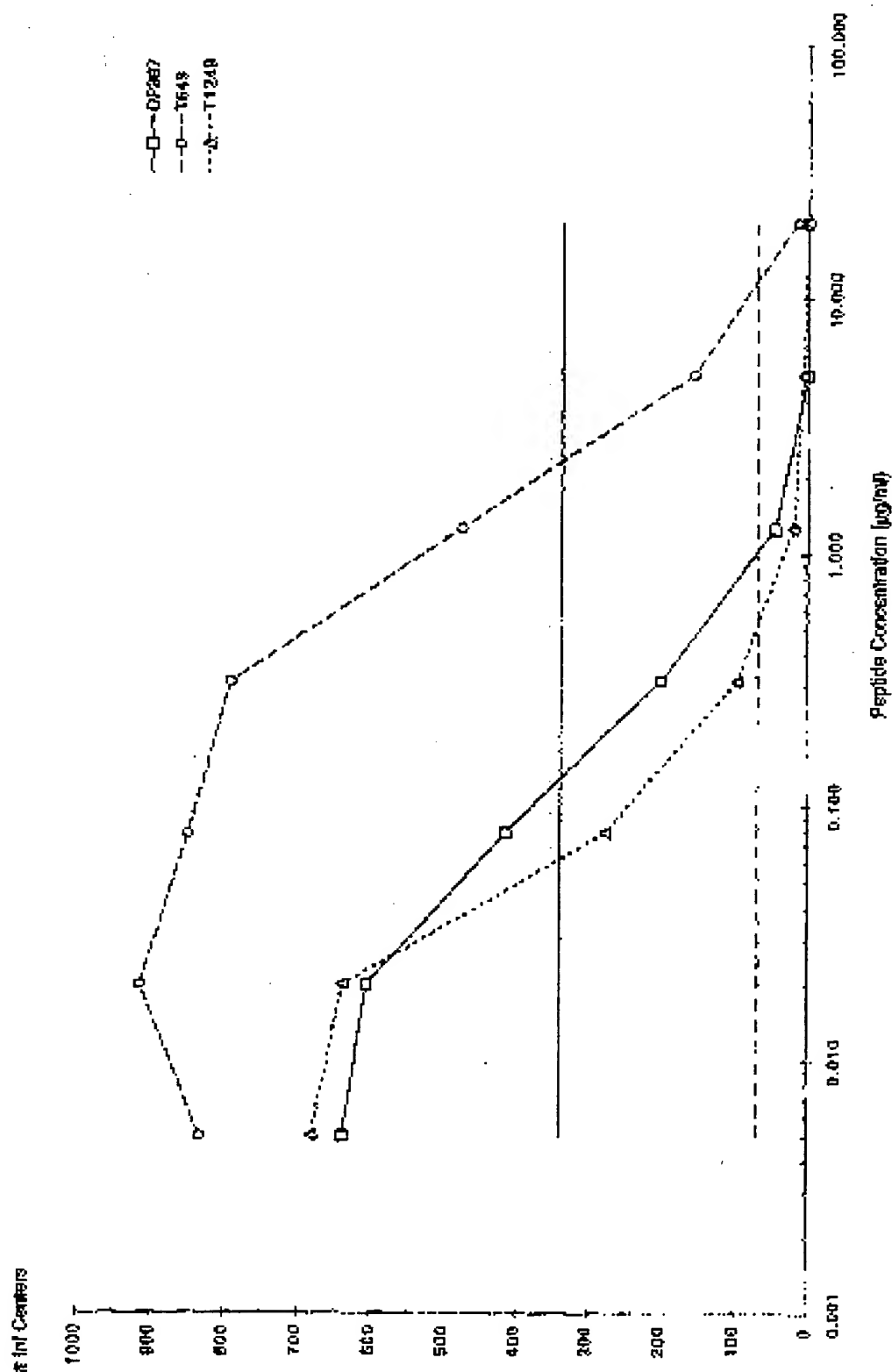


FIGURE 18D

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